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MD Research News

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Drug treatment

Ophthalmology. 2013 May 3. pii: S0161-6420(13)00331-X. doi: 10.1016/j.ophtha.2013.03.046. [Epub ahead of print]

Seven-Year Outcomes in Ranibizumab-Treated Patients in ANCHOR, MARINA, and HORIZON: A Multicenter Cohort Study (SEVEN-UP).

Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K; SEVEN-UP Study Group.

Department of Ophthalmology, School of Medicine, University of California, San Francisco, San Francisco, California.

PURPOSE: To assess long-term outcomes 7 to 8 years after initiation of intensive ranibizumab therapy in exudative age-related macular degeneration (AMD) patients.

DESIGN: Multicenter, noninterventional cohort study.

PARTICIPANTS: Sixty-five AMD patients originally treated with ranibizumab in the phase 3 Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trial, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) trial, and Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (HORIZON).

METHODS: Fourteen clinical trial sites recruited their original subjects for a return evaluation. Individual subject comparisons were obtained from the ANCHOR, MARINA, and HORIZON databases.

MAIN OUTCOME MEASURES: The primary end point was percentage with best-corrected visual acuity (BCVA) of 20/70 or better; secondary outcomes included mean change in letter score compared with previous time points and anatomic results on fluorescein angiography, spectral-domain ocular coherence tomography (OCT), and fundus autofluorescence (FAF).

RESULTS: At a mean of 7.3 years (range, 6.3-8.5 years) after entry into ANCHOR or MARINA, 37% of study eyes met the primary end point of 20/70 or better BCVA, with 23% achieving a BCVA of 20/40 or better. Thirty-seven percent of study eyes had BCVA of 20/200 or worse. Forty-three percent of study eyes had a stable or improved letter score (≥0-letter gain) compared with ANCHOR or MARINA baseline measurements, whereas 34% declined by 15 letters or more, with overall a mean decline of 8.6 letters ($P<0.005$). Since exit from the HORIZON study, study eyes had received a mean of 6.8 anti-vascular endothelial growth factor (VEGF) injections during the mean 3.4-year interval; a subgroup of patients who received 11 or more anti-VEGF injections had a significantly better mean gain in letter score since HORIZON exit ($P<0.05$). Active exudative disease was detected by spectral-domain OCT in 68% of study

eyes, and 46% were receiving ongoing ocular anti-VEGF treatments. Macular atrophy was detected by FAF in 98% of eyes, with a mean area of 9.4 mm2; the area of atrophy correlated significantly with poor visual outcome (P<0.0001).

CONCLUSIONS: Approximately 7 years after ranibizumab therapy in the ANCHOR or MARINA trials, one third of patients demonstrated good visual outcomes, whereas another third had poor outcomes. Compared with baseline, almost half of eyes were stable, whereas one third declined by 15 letters or more. Even at this late stage in the therapeutic course, exudative AMD patients remain at risk for substantial visual decline.

PMID: 23642856 [PubMed - as supplied by publisher]

Ophthalmology. 2013 May;120(5 Suppl):S8-S10. doi: 10.1016/j.ophtha.2013.01.058.

Implications of the comparisons of age-related macular degeneration treatments trials on clinical practice: what have we learned?

Do DV.

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TOPIC: Discussion of Comparisons of Age-Related Macular Degeneration (AMD) Treatments Trials (CATT) results and the potential impact on neovascular AMD treatment.

CLINICAL RELEVANCE: Ranibizumab and bevacizumab are most commonly used for treatment of neovascular AMD. Although bevacizumab costs less, its use primarily has been based on retrospective studies without level 1 medical evidence. Thus, there was an unmet need to determine whether there is any difference in efficacy and safety between the 2 agents when used monthly or as needed (pro re nata [PRN]).

METHODS: Review of CATT (focusing on 1-year data because 2-year data were not released at the time of this symposium), a randomized clinical trial evaluating the efficacy and safety of monthly and PRN dosing of ranibizumab and bevacizumab.

RESULTS: At the 1-year primary end point, eyes that received monthly ranibizumab gained an average of 8.5 letters; those that received monthly bevacizumab gained a mean of 8 letters. Eyes randomized to PRN ranibizumab gained an average of 6.8 letters; those randomized to PRN bevacizumab gained a mean of 5.9 letters. In the pairwise comparisons, PRN bevacizumab compared with monthly bevacizumab and PRN bevacizumab compared with monthly ranibizumab both were found to be inconclusive. At the 2-year end point, eyes that received monthly ranibizumab gained an average of 8.8 letters; those that received monthly bevacizumab gained a mean of 7.8 letters; those randomized to PRN ranibizumab gained an average of 6.7 letters; those randomized to PRN bevacizumab gained a mean of 5 letters. A higher rate of serious systemic adverse events also was detected among bevacizumab-treated subjects.

CONCLUSIONS: The CATT demonstrated that PRN ranibizumab is equivalent to monthly ranibizumab at the 1-year primary outcome. Monthly bevacizumab also is equivalent to monthly ranibizumab at the 1-year end point. The 2-year data showed less visual acuity gain with PRN dosing of either drug than monthly dosing.

PMID: 23642785 [PubMed - in process]

Ophthalmology. 2013 May;120(5 Suppl):S3-7. doi: 10.1016/j.ophtha.2013.01.057.

Current anti-vascular endothelial growth factor dosing regimens: benefits and burden.

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TOPIC: To examine the outcomes of clinical trials and case studies that investigated the different dosing regimens used for the 3 intravitreal anti-vascular endothelial growth factor (VEGF) inhibitors that are available currently. The Comparisons of Age-Related Macular Degeneration (AMD) Treatments Trial (CATT) data are discussed briefly here and are reviewed in greater detail in a separate accompanying article.

CLINICAL RELEVANCE: Sustained improvement with the 2 most widely used anti-VEGF drugs, bevacizumab and ranibizumab, requires monthly visits, posing a difficulty for patients. Thus, there is a need to evaluate whether individualized treatment regimens may reduce patient burden and improve patient outcomes.

METHODS: Review of clinical trials and case studies presented at recent medical conferences and published in peer-reviewed literature.

RESULTS: Numerous trials, including the Efficacy and Safety of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization (CNV) Secondary to AMD, Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intraocular Ranibizumab, Study of Ranibizumab in Patients with Subfoveal CNV Secondary to AMD, Extension Study to Evaluate the Safety and Tolerability of Ranibizumab in Subjects with CNV Secondary to AMD or Macular Edema Secondary to Retinal Vein Occlusion, Safety Assessment of Intravitreal Lucentis for AMD, and CATT, have evaluated alternatives to monthly dosing. Evidence suggests that either a treat-as-needed or, possibly, a treat-and-extend regimen provides a reasonable approach to monthly injections recommended for bevacizumab and ranibizumab, with the caveat that as yet, careful and ongoing surveillance remains a key feature of optical management.

CONCLUSIONS: Individualization of antiangiogenic treatment using data from clinical trials evaluating various dosing regimens against the patient's disease, lifestyle, and economic restrictions continues to evolve.

PMID: 23642784 [PubMed - in process]

Ophthalmology. 2013 May;120(5 Suppl):S23-5. doi: 10.1016/j.ophtha.2013.01.059.

Neovascular age-related macular degeneration: individualizing therapy in the era of anti-angiogenic treatments.

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Abstract: The treatment of neovascular age-related macular degeneration (AMD) had been revolutionized by the use of anti-vascular endothelial growth factor (VEGF) drugs: bevacizumab and ranibizumab. With the introduction of a third anti-VEGF drug, aflibercept, ophthalmologists have several options to choose from, as well as various treatment regimens they can follow. In this Interview, Jeffrey S. Heier, MD, of Ophthalmic Consultants of Boston, Massachusetts, discusses his approaches to managing the treatment of patients with AMD and providing them with individualized care.

PMID: 23642783 [PubMed - in process]

Ophthalmology. 2013 May;120(5 Suppl):S16-22. doi: 10.1016/j.ophtha.2013.01.060.

Putting theories and results into practice: managing cases.

Nguyen QD, Do DV, Haller JA, Heier JS, Kaiser PK.

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Abstract: The following are highlights from a case discussion, which was moderated by the Course Director, Quan Dong Nguyen, MD, MSc. The faculty reviewed 3 case studies and discussed their different approaches to managing the treatment of each patient. They also fielded questions from audience members about their management suggestions and the potential US Food and Drug Administration approval of aflibercept, which was not approved at the time of this discussion. In addition, the 2-year CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) results and 1-year IVAN (Inhibit Vascular Endothelial Growth Factor in Age-Related Choroidal Neovascularization) results were not released at the time this discussion took place.

PMID: 23642782 [PubMed - in process]

Ophthalmology. 2013 May;120(5 Suppl):S11-5. doi: 10.1016/j.ophtha.2013.01.061.

Emerging therapies for neovascular age-related macular degeneration: drugs in the pipeline.

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TOPIC: Discuss the emerging therapies that could improve the treatment of neovascular age-related macular degeneration (AMD).

CLINICAL RELEVANCE: Current antiangiogenic therapies require frequent injections, and not all patients respond to these therapies. Thus, there is a need to identify additional therapies that could improve the treatment of neovascular AMD.

METHODS: Review of medical literature and ongoing clinical trials as well as their results in the area of neovascular AMD treatment.

RESULTS: There are numerous areas of investigation into new treatment for AMD, including the newly approved aflibercept eye; sustained-release compounds that may allow for fewer injections, combination therapy with anti-vascular endothelial growth factor (VEGF) therapy and ionizing radiation, and investigational drugs that address different targets along the angiogenic signaling cascade, or other pathways related to the pathophysiology of neovascular AMD altogether.

CONCLUSIONS: Despite the outstanding advances made in the treatment of neovascular AMD with anti-VEGF therapies, patients still require numerous injections and office visits. Future therapies, however, have the potential not only to reduce patient visits and injections, but also to improve outcomes by targeting additional pathways, increasing target affinity, and lengthening treatment durability.

PMID: 23642781 [PubMed - in process]

Eur J Ophthalmol. 2013 May 3:0. doi: 10.5301/ejo.5000299. [Epub ahead of print]

Accessibility as a conditioning factor in treatment for exudative age-related macular degeneration.

Real JP, Luna JD, Urrets-Zavalia JA, De Santis MO, Palma SD, Granero GE.

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Purpose: Ranibizumab and bevacizumab coexist as the main therapeutic strategies for the treatment of neovascular age-related macular degeneration (NV-AMD). In Argentina, the access pathways to the drugs are different. Patients with different pathways and gatekeepers to access may experience different outcomes. The purpose of this work was to estimate the impact on therapeutic effects and visual outcome of the different accessibilities to NV-AMD treatment.

Methods: A retrospective analysis of the charts of 78 patients with previously untreated exudative AMD, who were treated with ranibizumab or bevacizumab between January 2009 and December 2011, was conducted. The main outcomes measured included time delay and change in mean best-corrected visual acuity (BCVA) between diagnosis and treatment and mean BCVA change at 1-year follow-ups.

Results: The delay between diagnosis and treatment and decrease in visual acuity over this time was significantly higher for patients treated with ranibizumab. At 1 year after the initiation of treatment, BCVA had a mean increase from baseline of 0.11 letters in the bevacizumab group with a mean of 4.71 injections, compared with a decrease of 8.87 letters with a mean of 2.98 injections in the ranibizumab group.

Conclusions: Access to treatment can be a key factor for success of therapy. Waiting times and availability of doses are crucial in the treatment of NV-AMD. Solving the problems related to delayed initiation of therapy and the difficulties in the maintenance phase are more important than define whether bevacizumab or ranibizumab is used.

PMID: 23661541 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 May 9. pii: iovs.12-11494v1. doi: 10.1167/iovs.12-11494. [Epub ahead of print]

Intravitreal Injection of Ranibizumab for Recovery of Macular Function in Eyes with Subfoveal Polypoidal Choroidal Vasculopathy.

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Purpose: To evaluate changes in macular function in eyes with polypoidal choroidal vasculopathy (PCV) after intravitreal ranibizumab (IVR) treatment.

Methods: Twenty-three eyes from 23 patients with treatment-naive subfoveal PCV received 3 monthly injections of IVR, followed by as-needed injections. Visual acuity (VA), retinal thickness (measured with optical coherence tomography), macular sensitivity (measured with microperimetry), and focal macular electroretinograms (fmERGs) were evaluated both before the initiation of therapy and after 3 and 12 months.

Results: Before treatment, cystoid macular edema was observed in 5 eyes, serous retinal detachments in 13 eyes, and serosanguinous pigment epithelial detachments in 18 eyes. IVR treatment resulted in substantial morphological improvements and consequent marked reductions in foveal thickness ($P = 0.008$). Although logMAR VA did not improve significantly over the 12-month study period ($P = 0.623$), the amplitude of the fmERG photopic negative response and macular sensitivity within 4 degree had increased significantly at 3 months ($P = 0.004$, $P = 0.026$, respectively). This trend persisted until the end of the 12-month monitoring period. Among the eyes with preexisting serous retinal detachments, those in which the detachments had resolved completely at 3 months also exhibited greater increases in fmERG a-wave amplitudes ($P = 0.048$).

Conclusion: IVR therapy resulted in morphological improvements and the partial recovery of macular function in eyes with subfoveal PCV. This therapy may improve photoreceptor function by resolving serous retinal detachments.

PMID: 23661367 [PubMed - as supplied by publisher]

J Mol Med (Berl). 2013 May 10. [Epub ahead of print]

An eye on the future of inflammasomes and drug development in AMD.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of central vision loss worldwide. While activation of the immune system has been implicated in disease progression, the pathways involved remain relatively unclear. Typically, inflammatory responses are caused as a result of pathogenic infection. However, in chronic conditions, like AMD, a form of 'sterile' inflammation can exist in localised areas of the body in response to modified host-derived elements and particulate matter accumulation, due to the activation of a complex termed the 'inflammasome'. Inflammasomes control the activity of two major pro-inflammatory cytokines, namely, interleukin (IL)-1β and IL-18, by allowing for their cleavage from inactive pro-forms into mature cytokines. The major pathological hallmark common to both 'dry' and 'wet' AMD is the presence of extracellular deposits, known as drusen, below the retinal pigment epithelium in the macula of the eye. Past studies have shown that host-derived particulate matter such as amyloid deposits and atherosclerotic plaques can be 'sensed' by the NLRP3-inflammasome causing cleavage of pro-IL-1β and pro-IL-18. We have recently reported that the NLRP3-inflammasome can also 'sense' drusen isolated from human AMD donor eyes and that IL-18 protects against the development of choroidal neovascularisation in a model that mimics 'wet' AMD. In fact, since then, a number of studies have reported roles for the NLRP3-inflammasome in AMD. This review will focus on describing, comparing and contrasting these reports and analyzing the potential for manipulating the NLRP3-inflammasome as a therapy for AMD.

PMID: 23661041 [PubMed - as supplied by publisher]

Ann Pharmacother. 2013 May 8. [Epub ahead of print]

Ranibizumab: The First Vascular Endothelial Growth Factor Inhibitor Approved for the Treatment of Diabetic Macular Edema (June).

Evoy KE, Abel SR.

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OBJECTIVE: To review the pharmacology, efficacy, and safety data available for ranibizumab and compare the drug to other therapeutic options for diabetic macular edema (DME) to determine its likely role in therapy.

DATA SOURCES: A PubMed search was initially used to identify all trials pertaining to the use of ranibizumab for DME. This search was conducted in February 2013 without a time frame for exclusion of older trials (all references included were published between January 1987 and February 2013. Following a review of the references of these articles, additional sources were obtained from PubMed, the man ufacturer's website, and clinicaltrials.gov.

STUDY SELECTION AND DATA EXTRACTION: Trials conducted in animals and those written in a language other than English were excluded. Abstracts of remaining trials were reviewed for determination

of relevance to this review. Preference was given to randomized controlled trials. Additional information sources were obtained from a review of references as deemed necessary by the authors.

DATA SYNTHESIS: Six Phase 2 or 3 randomized controlled trials studying the effects of ranibizumab in patients with DME were identified. Within these trials, ranibizumab consistently produced significantly greater gains in mean best corrected visual acuity than focal/grid laser photocoagulation or sham (7.4-12.5 letter improvement with ranibizumab vs 0.5-3 letters following focal/grid laser photocoagulation monotherapy) with a favorable safety and tolerability profile. Ranibizumab was also studied in combination with focal/grid laser photocoagulation, showing no additional gains in vision versus ranibizumab monotherapy.

CONCLUSIONS: The identified trials provide support for the safety and efficacy of ranibizumab in the treatment of vision loss due to DME and present a strong case for the shift to first-line treatment with vascular endothelial growth factor inhibitors from focal/grid laser photocoagulation, the standard of care since the Early Treatment Diabetic Retinopathy Study of 1985.

PMID: 23656749 [PubMed - as supplied by publisher]

Ophthalmology. 2013 May 1. pii: S0161-6420(13)00121-8. doi: 10.1016/j.ophtha.2013.02.002. [Epub ahead of print]

Cost-Effectiveness of Various Interventions for Newly Diagnosed Diabetic Macular Edema.

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OBJECTIVE: Anti-vascular endothelial growth factor therapies have revolutionized the treatment of clinically significant diabetic macular edema (CSDME); yet these agents are expensive, and whether they are cost-effective is unclear. The purpose of this study is to determine the most cost-effective treatment option for patients with newly diagnosed CSDME: focal laser photocoagulation alone (L), focal laser plus intravitreal ranibizumab (L+R), focal laser plus intravitreal bevacizumab (L+B), or focal laser plus intravitreal triamcinolone (L+T) injections.

DESIGN: Cost-effectiveness analysis.

PARTICIPANTS: Hypothetical cohort of 57-year-old patients with newly diagnosed CSDME.

METHODS: By using a Markov model with a 25-year time horizon, we compared the incremental cost-effectiveness of treating patients with newly diagnosed CSDME using L, L+R, L+B, or L+T. Data came from the DRCRnet randomized controlled trial, the Medicare fee schedule, and the medical literature.

MAIN OUTCOME MEASURES: Costs, quality-adjusted life years (QALYs), and incremental costs per QALY gained.

RESULTS: Compared with L, the incremental cost-effectiveness of L+R and L+B was $89 903/QALY and $11 138/QALY, respectively. L+T was dominated by L. A probabilistic sensitivity analysis demonstrated that, at a willingness to pay (WTP) of $50 000/QALY, L was approximately 70% likely to be the preferred therapy over L+R and L+T. However, at a WTP of $100 000/QALY, more than 90% of the time, L+R therapy was the preferred therapy compared with L and L+T. In the probabilistic sensitivity analysis, L+B was found to be the preferred therapy over L and L+T for any WTP value >$10 000/QALY. Sensitivity analyses revealed that the annual risk of cerebrovascular accident would have to be at least 1.5% higher with L+B than with L+R for L+R to be the preferred treatment. In another sensitivity analysis, if patients require <8 injections per year over the remainder of the 25-year time horizon, L+B would cost <$100 000/QALY, whereas L+R would be cost-effective at a WTP of $100 000/QALY if patients require fewer than 0.45

injections per year after year 2.

CONCLUSION: With bevacizumab and ranibizumab assumed to have equivalent effectiveness and similar safety profiles when used in the management of CSDME, bevacizumab therapy confers the greatest value among the different treatment options for CSDME.

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Expert Opin Drug Discov. 2013 May 6. [Epub ahead of print]

The many facets of PEDF in drug discovery and disease: a diamond in the rough or split personality disorder?

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Introduction: Pigment epithelium-derived factor (PEDF) was discovered as a neurotrophic factor secreted by retinal pigment epithelial cells. A decade later, it re-emerged as a powerful angiogenesis inhibitor guarding ocular function. Since then, significant advances were made identifying PEDF's mechanisms, targets and biomedical applications.

Areas covered: The authors review several methodologies that have generated significant new information about the potential of PEDF as a drug. Furthermore, the authors review and discuss mechanistic and structure-function analyses combined with the functional mapping of active fragments, which have yielded several short bioactive PEDF peptides. Additionally, the authors present functional studies in knockout animals and human correlates that have provided important information about conditions amenable to PEDF-based therapies.

Expert opinion: Through its four known receptors, PEDF causes a wide range of cellular events vitally important for the organism, which include survival and differentiation, migration and invasion, lipid metabolism and stem cell maintenance. These processes are deregulated in multiple pathological conditions, including cancer, metabolic and cardiovascular disease. PEDF has been successfully used in countless preclinical models of these conditions and human correlates suggest a wide utility of PEDF-based drugs. The most significant clinical application of PEDF, to date, is its potential therapeutic use for age-related macular degeneration. Moreover, PEDF-based gene therapy has advanced to early stage clinical trials. PEDF active fragments have been mapped and used to design short peptide mimetics conferring distinct functions of PEDF, which may address specific clinical problems and become prototype drugs.

PMID: 23642051 [PubMed - as supplied by publisher]

Retina. 2013 May 6. [Epub ahead of print]

PROSPECTIVE EVALUATION OF THE INCIDENCE AND RISK FACTORS FOR THE DEVELOPMENT OF RPE TEARS AFTER HIGH- AND LOW-DOSE RANIBIZUMAB THERAPY.

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PURPOSE: To prospectively determine the incidence and risk factors for retinal pigment epithelial (RPE)

tears in eyes with vascularized pigment epithelial detachments (PED) and exudative age-related macular degeneration receiving antivascular endothelial growth factor therapy.

METHODS: Eyes were prospectively randomized into 1 of 4 arms: 1) 0.5 mg of ranibizumab monthly for 12 months; 2) 0.5 mg of ranibizumab monthly for 3 months and then pro re nata on the basis of clinical and optical coherence tomography-guided indications; 3) high-dose 2.0 mg of ranibizumab monthly for 12 months; or 4) 2.0 mg of ranibizumab monthly for 3 months and then pro re nata thereafter. All PEDs were measured for height, greatest linear diameter, and surface area at baseline. The incidence of RPE tears in the entire 4-arm cohort was determined at the end of 12 months. Eyes were divided into two groups (tear vs. nontear) and statistically compared to determine risk factors for the development of RPE tear.

RESULTS: Of 37 eyes, a total of 5 developed postranibizumab RPE tears during the course of the study (incidence 14%). Four of the 5 tears occurred in the high-dose 2.0-mg groups. Baseline PED height, surface area, and greatest linear diameter were significantly greater in the group that developed RPE tears versus the nontear group (P = 0.018, 0.031, and 0.048, respectively). There were significantly more eyes with PED height >550 microns in the RPE tear group (4 of 5, 80%) compared with the nontear group (9 of 32, 18%) (P = 0.042). The presence of PED height >550 microns was associated with an increased tear rate from 14% to 31%. Furthermore, retrospective identification of a ring sign or Grade 1 tear at baseline, in addition to PED height >550 microns, was associated with a further increase in the tear rate to 67%.

CONCLUSION: In this study, the prospective incidence of RPE tears was ~14%. A baseline PED height >550 microns and presence of a Grade 1 tear, or positive ring sign, were identified as high-risk factors for the subsequent development of an RPE tear.

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Acta Ophthalmol. 2013 May 7. doi: 10.1111/aos.12153. [Epub ahead of print]

Functional and morphological changes in diabetic macular edema over the course of anti-vascular endothelial growth factor treatment.

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Purpose: To evaluate macular morphology and function in diabetic macular edema (DME) over the course of intravitreal anti-vascular endothelial growth factor (VEGF) treatment with Ranibizumab.

Methods: A consecutive series of 39 study eyes with centre-involving DME were included in this study. In all subjects, best-corrected visual acuity (BCVA) according ETDRS protocol, fluorescein angiography (FA), microperimetric macular sensitivity (MP) and Spectral Domain optical coherence tomography (SD-OCT) cross-sectional scans were obtained before treatment and after 3 monthly applied intravitreal Ranibizumab injections. Six different morphological qualities [IS/OS layer integrity, outer nuclear layer (ONL) cysts, ONL cyst size, inner nuclear layer (INL) cysts, blocking phenomenon and subretinal fluid] were graded of each cross-sectional OCT scan before and over the course of treatment by two experienced graders. Correlation analyses between functional and morphological parameters were obtained.

Results: Mean BCVA increased from 26 ± 14 to 33 ± 13 letters after 3 consecutive monthly applied Ranibizumab injections ($p < 0.001$). Central retinal thickness (CRT) decreased from 504 ± 144 to 387 ± 122 µm ($p < 0.001$). Over the course of treatment, IS/OS continuity improved (index: 0.56 ± 0.52 to 0.43 ± 0.49, $Z = -1.415$, $p = 0.157$), ONL cyst prevalence and size decreased significantly (index: 0.61 ± 0.44 to 0.56 ± 0.35, $Z = -3.41$, $p = 0.001$ and 1.75 ± 0.88 to 1.17 ± 1.05, $Z = -4.02$, $p < 0.001$), INL cyst prevalence decreased (index: 0.35 ± 0.52 to 0.28 ± 0.52, $Z = -1.60$, $p = 0.109$), blocking phenomenon did not change significantly (index: 00.12 ± 0.16 to 0.13 ± 0.15, $Z = -0.45$, $p = 0.656$) and subretinal fluid almost disappeared (index: 0.10 ± 0.24 vs. 0.00 ± 0.01, $Z = -$

2.56, p = 0.011). Correlation analyses revealed highest significant correlations between ONL cyst prevalence and their size and CRT as well as BCVA and MP before treatment and over the course of treatment.

Conclusions: ONL cysts and their size as morphological parameters correlate with retinal function measured with BCVA and microperimetry before and over the course of anti-VEGF therapy with Ranibizumab in patients with DME.

PMID: 23647578 [PubMed - as supplied by publisher]

Ophthalmol Eye Dis. 2012 Mar 13;4:15-21. doi: 10.4137/OED.S7264. Print 2012.

Safety and Efficacy of Ranibizumab in Macular Edema following Retinal Vein Occlusion.

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Abstract: Macular edema is the leading cause of visual impairment in patients with retinal vein occlusion. Limited improvements may be obtained with laser photocoagulation or intravitreal triamcinolone. However, according to the data provided by randomized clinical trials, intravitreal injections of ranibizumab (Lucentis; Genentech, South San Francisco, CA) constitute a new effective and safe option for the management of these vision-threatening diseases. The aim of the present review is to summarize the clinical evidence of ranibizumab for macular edema due to retinal vein occlusions.

PMID: 23650454 [PubMed] PMCID: PMC3619496

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2013 May 7. pii: iovs.13-11891v1. doi: 10.1167/iovs.13-11891. [Epub ahead of print]

Blue-light Reflectance Imaging of Macular Pigment in Infants and Children.

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PURPOSE: While the role of the macular pigment carotenoids in the prevention of age-related macular degeneration has been extensively studied in adults, comparatively little is known about the physiology and function of lutein and zeaxanthin in the developing eye. We therefore developed a protocol using the RetCam to measure macular pigment optical density (MPOD) and distributions in premature infants and in children.

METHODS: We used blue light reflectance to image the macular pigment in premature babies at the time of ROP screening and in children under age seven who were undergoing examinations under anesthesia for other reasons. We correlated the MPOD with skin carotenoid levels measured by resonance Raman spectroscopy, serum carotenoids measured by HPLC, and dietary carotenoid intake.

RESULTS: We enrolled 51 infants and children ranging from preterm to age seven. MPOD correlated significantly with age (r=0.36; P=0.0142), with serum lutein+zeaxanthin (r=0.44; P=0.0049) and with skin carotenoid levels (r=0.42; P=0.0106) but not with dietary lutein+zeaxanthin intake (r=0.13; P=0.50). All premature infants had undetectable macular pigment, and most had unusually low serum and skin

carotenoid concentrations.

CONCLUSIONS: Our most remarkable finding is the undetectable MPOD in premature infants. This may be due in part to foveal immaturity, but the very low levels of serum and skin carotenoids suggest that these infants are carotenoid insufficient as a consequence of low dietary intake and/or severe oxidative stress. The potential value of carotenoid supplementation in the prevention of ROP and other disorders of prematurity should be a fruitful direction for further investigation.

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Macular Morphology and Visual Acuity in the Comparison of Age-related Macular Degeneration Treatments Trials.

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OBJECTIVE: To describe the effects of treatment for 1 year with ranibizumab or bevacizumab on macular morphology and the association of macular morphology with visual acuity (VA) in eyes with neovascular age-related macular degeneration (AMD).

DESIGN: Prospective cohort study within a randomized clinical trial.

PARTICIPANTS: Participants in the Comparison of Age-related Macular Degeneration Treatments Trials.

METHODS: Participants were assigned randomly to treatment with ranibizumab or bevacizumab on a monthly or as-needed schedule. Optical coherence tomography (OCT), fluorescein angiography (FA), color fundus photography (FP), and VA testing were performed periodically throughout 52 weeks. Masked readers graded images. General linear models were applied to evaluate effects of time and treatment on outcomes.

MAIN OUTCOME MEASURES: Fluid type and location and thickness by OCT, size, and lesion composition on FP, FA, and VA.

RESULTS: Intraretinal fluid (IRF), subretinal fluid (SRF), subretinal pigment epithelium fluid, and retinal, subretinal, and subretinal tissue complex thickness decreased in all treatment groups. A higher proportion of eyes treated monthly with ranibizumab had fluid resolution at 4 weeks, and the difference persisted through 52 weeks. At 52 weeks, there was little association between the presence of fluid of any type (without regard to fluid location) and the mean VA. However, at all time points, eyes with residual IRF, especially foveal IRF, had worse mean VA (9 letters) than those without IRF. Eyes with abnormally thin (<120 μm) or thick (>212 μm) retinas had worse VA than those with normal thickness (120-212 μm). At week 52, eyes with larger neovascular lesions or with foveal scar had worse VA than eyes without these features.

CONCLUSIONS: Anti-vascular endothelial growth factor (VEGF) therapy reduced lesion activity and improved VA in all treatment groups. At all time points, eyes with residual IRF had worse VA than those without. Eyes with abnormally thin or thick retinas, residual large lesions, and scar also had worse VA. Monthly ranibizumab dosing yielded more eyes with no fluid and an abnormally thin retina, although the long-term significance is unknown. These results have important treatment implications in eyes undergoing anti-VEGF therapy for neovascular AMD.

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Localized reticular pseudodrusen and their topographic relation to choroidal watershed zones and changes in choroidal volumes.

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PURPOSE: We identified a topographic relation of localized reticular pseudodrusen (RPD) to choroidal watershed zones (CWZ) and to changes in choroidal volumes (CV).

METHODS: We included 30 eyes of 30 patients with RPD in an area <10 mm(2) and no other retinal alteration (76.7 ± 6.9 years). Patients underwent spectral-domain optical coherence tomography (SD-OCT), enhanced depth imaging (EDI) OCT, fluorescein video-angiography (vFA), indocyanine green video-angiography (vICG), and confocal scanning laser ophthalmoscopy (cSLO). vICG was evaluated for the presence, localization, and configuration of CWZ. Retinal areas affected by RPD were measured, and their localization was determined in relation to CWZ. CV was measured using a choroidal thickness map of the posterior pole and the Early Treatment of Diabetic Retinoscopy Study (ETDRS) grid.

RESULTS: In all study eyes, RPD could be demonstrated clearly in SD-OCT, EDI-OCT, FA, ICG, and cSLO. CWZ were identified in 25 eyes (83.3%). The area affected by RPD was 7.45 ± 2.25 mm(2). RPD area was located fully or partly within the CWZ in 22 eyes (88.0%). Mean CV in the full ETDRS grid area was reduced significantly (4.49 ± 1.44 mm(3)). Foveal CV and CV in the grid sector affected mostly by RPD were significantly diminished to 0.14 ± 0.05 mm(3) and 0.85 ± 0.38 mm(3), respectively.

CONCLUSIONS: The site of localized RPD seems to be related to presence and site of CWZ, suggesting that choroidal hypoxia may have a role in RPD pathogenesis. Reduced CV in eyes with localized RPD could be demonstrated and may be cause or consequence of RPD development.

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Improving Function in Age-Related Macular Degeneration: A Randomized Clinical Trial.

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PURPOSE: To compare the efficacy of problem-solving therapy (PST) with supportive therapy (ST) to improve targeted vision function (TVF) in age-related macular degeneration (AMD).

DESIGN: Single-masked, attention-controlled, randomized clinical trial with outcome assessments at 3 months (main trial endpoint) and 6 months (maintenance effects).

PARTICIPANTS: Patients with AMD (n = 241) attending retina practices.

INTERVENTIONS: Whereas PST uses a structured problem-solving approach to reduce vision-related task difficulty, ST is a standardized attention-control treatment.

MAIN OUTCOME MEASURES: We assessed TVF, the 25-item National Eye Institute Vision Function Questionnaire plus Supplement (NEI VFQ), the Activities Inventory (AI), and vision-related quality of life (QoL).

RESULTS: There were no between-group differences in TVF scores at 3 (P = 0.47) or 6 (P = 0.62) months.

For PST subjects, mean ± standard deviation TVF scores improved from 2.71±0.52 at baseline to 2.18±0.88 at 3 months (P = 0.001) and were 2.18±0.95 at 6 months (change from 3 to 6 months, P = 0.74). For ST subjects, TVF scores improved from 2.73±0.52 at baseline to 2.14±0.96 at 3 months (P = 0.001) and were 2.15±0.96 at 6 months (change from 3 to 6 months, P = 0.85). Similar proportions of PST and ST subjects had less difficulty performing a TVF goal at 3 months (77.4% vs 78.6%, respectively; P = 0.83) and 6 months (76.2% vs 79.1%, respectively; P = 0.61). There were no changes in the NEI VFQ or AI. Vision-related QoL improved for PST relative to ST subjects at 3 months (F(4, 192) = 2.46; P = 0.05) and at 6 months (F(4, 178) = 2.55; P = 0.05). The PST subjects also developed more adaptive coping strategies than ST subjects.

CONCLUSIONS: We found that PST was not superior to ST at improving vision function in patients with AMD, but that PST improved their vision-related QoL. Despite the benefits of anti-vascular endothelial growth factor treatments, AMD remains associated with disability, depression, and diminished QoL. This clinical reality necessitates new rehabilitative interventions to improve the vision function and QoL of older persons with AMD.

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Introduction: neovascular age-related macular degeneration: approaches for improving visual acuity and reducing the burden of care.

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Pathogenesis

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Zinc-induced self-association of complement C3b and Factor H: implications for inflammation and age-related macular degeneration.

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Abstract: The sub-retinal pigment epithelial deposits (sRPEds) that are a hallmark of age-related macular degeneration (AMD) contain both C3b and mM levels of zinc. C3 is the central protein of complement, while C3u is formed by the spontaneous hydrolysis of the thioester bridge in C3. During activation, C3 is cleaved to form active C3b, then C3b is inactivated by Factor I and Factor H to form the C3c and C3d fragments. The interaction of zinc with C3 was quantified using analytical ultracentrifugation and X-ray scattering. C3, C3u, and C3b associated strongly in >100 μM [Zn], while C3c and C3d showed weak association. With zinc, C3 forms soluble oligomers, while C3u and C3b precipitate. We conclude that the C3, C3u and C3b association with zinc depended on the relative positions of C3d and C3c in each protein. Computational predictions showed that putative weak zinc binding sites with different capacities exist in all five proteins, in agreement with experiment. Factor H forms large oligomers in >10 μM [Zn]. In distinction to C3b or Factor H alone, the solubility of the central C3b-Factor H complex was much reduced at 60 μM [Zn], and even more so at >100 μM [Zn]. The removal of the C3b-Factor H complex by zinc explains the reduced C3u/C3b inactivation rates by zinc. Zinc-induced precipitation may contribute to the initial development of sRPEds in

the retina, as well as reducing the progression to advanced AMD in higher-risk patients.

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Rat retinal transcriptome: Effects of aging and AMD-like retinopathy.

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Abstract: Pathogenesis of age-related macular degeneration (AMD), the leading cause of vision loss in the elderly, remains poorly understood due to the paucity of animal models that fully replicate the human disease. Recently, we showed that senescence-accelerated OXYS rats develop a retinopathy similar to human AMD. To identify alterations in response to normal aging and progression of AMD-like retinopathy, we compared gene expression profiles of retina from 3- and 18-mo-old OXYS and control Wistar rats by means of high-throughput RNA sequencing (RNA-Seq). We identified 160 and 146 age-regulated genes in Wistar and OXYS retinas, respectively. The majority of them are related to the immune system and extracellular matrix turnover. Only 24 age-regulated genes were common for the two strains, suggestive of different rates and mechanisms of aging. Over 600 genes showed significant differences in expression between the two strains. These genes are involved in disease-associated pathways such as immune response, inflammation, apoptosis, Ca (2+) homeostasis and oxidative stress. The altered expression for selected genes was confirmed by qRT-PCR analysis. To our knowledge, this study represents the first analysis of retinal transcriptome from young and old rats with biologic replicates generated by RNA-Seq technology. We can conclude that the development of AMD-like retinopathy in OXYS rats is associated with an imbalance in immune and inflammatory responses. Aging alters the expression profile of numerous genes in the retina, and the genetic background of OXYS rats has a profound impact on the development of AMD-like retinopathy.

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Brain. 2013 Feb 8. [Epub ahead of print]

Reply: Microcystic macular degeneration from optic neuropathy: not inflammatory, not trans-synaptic degeneration.

Gelfand JM, Green AJ.

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Genetics

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Variants at chromosome 10q26 locus and the expression of HTRA1 in the retina.

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Abstract: Variations in a locus at chromosome 10q26 are strongly associated with the risk of age-related macular degeneration (AMD). The most significantly associated haplotype includes a nonsynonymous SNP rs10490924 in the exon 1 of ARMS2 and rs11200638 in the promoter region of HTRA1. It is under debate which gene(s), ARMS2, HTRA1 or some other genes are functionally responsible for the genetic association. To verify whether the associated variants correlate with a higher HTRA1 expression level as previously reported, HTRA1 mRNA and protein were measured in a larger human retina-RPE-choroid samples (n = 82). Results show there is no significant change of HTRA1 mRNA level among genotypes at rs11200638, rs10490924 or an indel variant of ARMS2. Furthermore, two AMD-associated synonymous SNPs rs1049331 and rs2293870 in HTRA1 exon 1 do not change its protein level either. These results suggest that the AMD-associated variants in the chromosome 10q26 locus do not significantly affect the expression of HTRA1.

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Diet

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A systematic review on zinc for the prevention and treatment of age-related macular degeneration.

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PURPOSE: The objective of this systematic review was to examine the evidence on zinc intake from foods and supplements in the primary prevention and treatment of Age-related macular degeneration (AMD).

METHODS: Randomized controlled trials (RCTs), prospective cohort, retrospective cohort and case-control studies that investigated zinc intake from foods and/or supplements and AMD in men and women with a mean age of >50 y were included. Medline® and Cochrane Central were searched from inception to February 2012 and November 2012, respectively. Data extraction and quality appraisal were done on all eligible studies.

RESULTS: Ten studies were included: 4 RCTs, 4 prospective cohort and 2 retrospective cohort studies. Age-related Eye Disease Study (AREDS) showed zinc treatment to significantly reduce the risk of progression to advanced AMD. The risk of visual acuity loss was of similar magnitude but not statistically significant. Two RCTs reported statistically significant increases in visual acuity in early AMD patients and one RCT showed no effect of zinc treatment on visual acuity in advanced AMD patients. Results from 6 cohort studies on associations between zinc intake and incidence of AMD were inconsistent.

CONCLUSIONS: Current evidence on zinc intake for the prevention of AMD is inconclusive. Based on the strength of AREDS we can conclude that zinc treatment may be effective in preventing progression to advanced AMD. Zinc supplementation alone may not be sufficient to produce clinically meaningful changes in visual acuity.

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Precursors of Age-Related Macular Degeneration: Associations with Physical Activity, Obesity and Serum Lipids in the Inter99 Eye Study.

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PURPOSE: To investigate associations of small, hard macular drusen and larger macular drusen with obesity-related risk factors.

METHODS: Cross-sectional study of 888 subjects aged 30-60 years characterized using anthropometric measurements and blood sample analyses. Physical activity was assessed by questionnaire. Digital grayscale fundus photographs were recorded in red-free illumination and graded for the presence of macular drusen >63µm in either eye and the presence of 20 or more small, hard macular drusen as a mean of both eyes.

RESULTS: Macular drusen >63µm were associated with the level of physical activity, the age- and sex adjusted odds ratio being 0.33 (95% confidence interval 0.13-0.82, P=0.016) for participants who were physically active more than 7 h/week compared with participants active 0-2 h/week. In women, macular drusen >63µm were associated with higher serum triglycerides (P=0.0005). A waist circumference in the top quartile increased the odds for drusen >63µm in men whereas in women having a waist circumference in the middle quartiles reduced these odds. The presence of 20 or more small, hard macular drusen was associated with lower levels of serum high-density lipoprotein cholesterol (HDL) (P=0.029) and with moderately elevated triglycerides.

CONCLUSIONS: Precursors of AMD were associated with modifiable obesity-related risk factors, notably low physical activity with drusen >63 µm and lower serum HDL and moderately elevated serum triglycerides with 20 or more small, hard macular drusen per eye. These findings support that a physically active, heart-healthy lifestyle prevents the earliest manifestation of AMD.

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J Photochem Photobiol B. 2013 Apr 18;124C:34-41. doi: 10.1016/j.jphotobiol.2013.04.003. [Epub ahead of print]

Silk lutein extract and its combination with vitamin E reduce UVB-mediated oxidative damage to retinal pigment epithelial cells.

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Abstract: Increased exposure to solar ultraviolet B (UVB) radiation may promote age related macular degeneration (AMD). Lutein can protect retinal pigment epithelial (RPE) cells from various oxidative insults but its direct protection against UVB has not been reported. This study aimed to demonstrate protective effects of silk lutein extract against UVB-induced oxidative damage to RPE cells and compared with standard lutein and Trolox, a vitamin E analog. ARPE-19 cells were treated with luteins with and without Trolox prior to UVB exposure. Cell viability and apoptosis were determined by trypan blue staining and caspase-3 activity, respectively. Oxidative damage was evaluated by measuring intracellular reactive oxygen species (ROS), lipid peroxidation, and activities of antioxidant enzymes (superoxide dismutase, glutathione peroxidase and catalase). Levels of lutein remained in culture medium was determined by HPLC. Both luteins reduced cellular ROS levels and lipid peroxidation mediated by UVB, and subsequently increased cell viability and reduced apoptosis. They also restored activities of most tested antioxidant enzymes. Enhancement of lutein antioxidant efficacy was observed in the presence of Trolox. In all these effects, the two lutein preparations had similar effectivenesses. In cell free media, Trolox enhanced the

protective effect of lutein probably by reducing its degradation and repairing the oxidized derivatives. Yellow silk cocoon is a potential candidate of lutein for further development as dietary supplement for the prevention of AMD.

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