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MD Research News

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Drug treatment

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Predictive Value of Retinal Morphologic Features for Visual Acuity Outcomes of Different Ranibizumab Treatment Regimens for Neovascular Age-Related Macular Degeneration.

Waldstein SM, Wright J, Warburton J, Margaron P, Simader C, Schmidt-Erfurth U.

PURPOSE: To establish the predictive value of defined retinal morphologic parameters on visual outcomes and re-treatment needs in patients with neovascular age-related macular degeneration (nAMD) receiving ranibizumab treatment.

DESIGN: Post hoc analysis of a prospective, 12-month, multicenter, phase IIIb trial.

PARTICIPANTS: Three hundred fifty-three treatment-naïve patients with nAMD.

METHODS: Available data from 319 treatment-naïve patients receiving ranibizumab 0.3 mg monthly (frequent regimen; n = 102) or ranibizumab 0.3 or 0.5 mg quarterly (pooled 0.3/0.5 mg = infrequent regimen; n = 217) were analyzed to assess the correlations between baseline retinal morphologic parameters and best-corrected visual acuity (BCVA) change (structure-function correlations). The BCVA was measured at monthly visits. Optical coherence tomography scans were acquired monthly for quantitative measures of the central retinal thickness and qualitative assessment of retinal morphologic features. Assessed morphologic parameters included intraretinal cystoid fluid (IRC), subretinal fluid (SRF), pigment epithelial detachment, and vitreomacular interface configuration classification comprising vitreomacular adhesion and posterior vitreous detachment (PVD). An analysis of covariance was conducted to evaluate the impact of retinal morphologic features on BCVA change at month 12.

MAIN OUTCOME MEASURES: Change in BCVA from baseline to month 12 compared between frequent and infrequent treatment arms.

RESULTS: Relevant predictive factors for BCVA change at month 12 were baseline SRF (P = 0.05), PVD (P = 0.03), IRC (P = 0.05), treatment frequency (P < 0.01), and BCVA (P < 0.01). The presence of both SRF and PVD at baseline was associated with similar BCVA gains regardless of treatment frequency (mean difference in BCVA gains at month 12 of +2.6 letters in favor of infrequent treatment). Subretinal fluid was present in 71% of patients, and PVD was present in 64% of patients.

CONCLUSIONS: In patients with both SRF and PVD at baseline, similar BCVA outcomes were observed regardless of treatment frequency. These patients may require less frequent treatments compared with patients without SRF, without PVD, or without either who may require more frequent injections for maintenance of vision. This finding may have implications in clinical practice by helping to tailor an individualized re-treatment interval in nAMD patients.

PMID: 26481821 [PubMed - as supplied by publisher]

J Ophthalmol. 2015;2015:820605. Epub 2015 Sep 27.

Long-Term Visual Outcome in Wet Age-Related Macular Degeneration Patients Depending on the Number of Ranibizumab Injections.

Calvo P, Abadia B, Ferreras A, Ruiz-Moreno O, Leciñena J, Torrón C.

Purpose: To analyse the visual outcome in wet age-related macular degeneration (AMD) patients depending on the number of ranibizumab injections.

Methods: 51 naïve wet AMD patients were retrospectively recorded. Visual acuity (VA), central retinal thickness (CRT) measured with spectral domain (SD) optical coherence tomography (OCT), and number of intravitreal injections were compared at 6, 12, 18, 24, 30, and 36 months of follow-up. Kaplan-Meier survival rates (SRs) based on VA outcomes were calculated depending on the number of ranibizumab injections performed.

Results: VA improved compared with baseline at 6 and 12 months ($P < 0.005$). No differences were found at 18, 24, 30, and 36 months ($P > 0.05$). CRT measured with Cirrus OCT decreased ($P < 0.001$) at all time points analysed. The mean number of injections received was 6.98 ± 3.69. At 36 months, Kaplan-Meier SR was 76.5% (the proportion of patients without a decrease in vision of more than 0.3 logMAR units). VA remained stable (≤0.01 logMAR units) or improved in 62.7%. Within this group, SR was 92.9% in those who received 7 or more injections versus 51.4% receiving <7 treatments ($P = 0.008$; log-rank test).

Conclusion: Better VA outcomes were found in stable wet AMD patients after 3 years of follow-up if they received ≥7 ranibizumab injections.

PMID: 26491555 [PubMed] PMCID: PMC4600568

J Ophthalmol. 2015;2015:412903. Epub 2015 Sep 27.

Individualized Therapy with Ranibizumab in Wet Age-Related Macular Degeneration.

García-Layana A, Figueroa MS, Arias L, Araiz J, Ruiz-Moreno JM, García-Arumí J, Gómez-Ulla F, López-Gálvez MI, Cabrera-López F, García-Campos JM, Monés J, Cervera E, Armadá F, Gallego-Pinazo.

Abstract: Individualized treatment regimens may reduce patient burden with satisfactory patient outcomes in neovascular age-related macular degeneration. Intravitreal anti-VEGF drugs are the current gold standard. Fixed monthly injections offer the best visual outcome but this regimen is not commonly followed outside clinical trials. A PRN regimen requires monthly visits where the patient is treated in the presence of signs of lesion activity. Therefore, an early detection of reactivation of the disease with immediate retreatment is crucial to prevent visual acuity loss. Several trials suggest that "treat and extend" and other proactive regimens provide a reasonable approach. The rationale of the proactive regimens is to perform treatment anticipating relapses or recurrences and therefore avoid drops in vision while individualizing patient followup. Treat and extend study results in significant direct medical cost savings from fewer treatments and office visits compared to monthly treatment. Current data suggest that, for one year, PRN is less expensive, but treat and extend regimen would likely be less expensive for subsequent years. Once a patient is not a candidate to continue with treatment, he/she should be sent to an outpatient unit with adequate resources to follow nAMD patients in order to reduce the burden of specialized ophthalmologist services.

PMID: 26491550 [PubMed] PMCID: PMC4600506

Eye (Lond). 2015 Oct 23. [Epub ahead of print]

South Asian diabetic macular oedema treated with ranibizumab (ADMOR)-real-life experience.

Ghanchi F, Hazel CA.

Purpose: Diabetic macular oedema (DMO) is a leading cause for visual impairment in the working age population in the UK. Ranibizumab has been shown to be effective in treatment of DMO in studies based on mainly Caucasian populations. This study reports the 12-month outcome in a cohort of South Asian subjects with DMO treated with ranibizumab.

Methods: DMO in 51 eyes of 41 South Asian patients was treated with ranibizumab 0.5 mg according to the modified DRCRnet protocol I. Visual acuity (VA) and central macular thickness (CMT) were recorded at baseline, 3, 6, and 12 months. Results were compared for eyes with different baseline visual acuities and different baseline macular thicknesses.

Results: Over the 12-month period, the mean ETDRS VA increased from 55.3±13.4 letters to 63.8±15.2 letters for all eyes. At 12 months, 70.6% eyes gained 5 or more letters acuity and 17.6% eyes gained 15 letters or more. During the same period, the mean CMT decreased from 532±129 to 318±136 μm. Eyes that had received previous laser treatments had a mean letter gain of 9.2 letters, compared with 8.5 for all eyes at 12 months.

Conclusions: Ranibizumab 0.5 mg is safe and effective at reversing vision loss due to DMO in patients of South Asian origin at 12 months. Ranibizumab treatment appears to be effective in patients with longstanding DMO who received prior laser treatments. Further studies are needed to define the long-term outcome in patients of different ethnicity and DMO.

PMID: 26493032 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2015 Oct 21;15(1):138.

Intravitreal treatment in patients with exudative age-related macular degeneration and visual acuity ≤ 0.05.

Koch R, Schmidt M, Gebauer S, Busse H, Uhlig CE.

BACKGROUND: To investigate intravitreal treatment efficiencies in patients suffering from exudative ARMD with a BCVA ≤ 0.05.

METHODS: Retrospective analysis: Analysis parameters were lesion type, BCVA at baseline and at follow-up, the intravitreal drug used, and its application frequency. Patients were divided into: 1) following injections of bevacizumab, triamcinolone, their combination, or ranibizumab regardless of their lesion subtype, 2) or by lesion subtype. Statistical tests were performed using Wilcoxon signed-rank tests, Kruskal -Wallis tests and multivariable logistic regressions.

RESULTS: Seventy four eyes of 74 patients were analyzed. Follow-up was at 12.0 to 15.7 weeks. Median difference of BCVA (logMAR) between baseline and follow-up was 0.000 (-0.030, 0.175) in classic (p = 0.105), 0.000 (-1.15, 0.20) in occult (p = 0.005), -0.200 (-1.20, 0.60) in cases with subretinal fluid (p = 0.207), 0.000 (-0.60, 0.30) in pigment epithelial detachment (p = 0.813), and 0.050 (-0.40, 0.70) in Junius Kuhnt maculopathy (p = 0.344). BCVA increased ≥ 0.2 logMAR in 4 (24 %) classic, 9 (47 %) occult, 6 (33 %) pigment epithelial detachment, 6 (55 %) subretinal fluid, in 29 (39 %) eyes regardless of the lesion type, and reached a BCVA ≥ 0.05 in 7 (9 %) of those with a baseline BCVA <0.05.

CONCLUSIONS: Results indicate that in patients with ARMD and a BCVA lower 0.05, intravitreal treatment may improve visual acuity, most probably in cases with occult lesions.

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Ophthalmology. 2015 Oct 15. [Epub ahead of print]

Intravitreal Bevacizumab Versus Ranibizumab for Treatment of Neovascular Age-Related Macular Degeneration: Findings from a Cochrane Systematic Review.

Solomon SD, Lindsley KB, Krzystolik MG, Vedula SS, Hawkins BS.

TOPIC: To summarize the relative effects of bevacizumab (Avastin; Genentech, Inc, South San Francisco, CA) and ranibizumab (Lucentis; Genentech, Inc.), using findings from a Cochrane Eyes and Vision Group systematic review.

CLINICAL RELEVANCE: Neovascular age-related macular degeneration (NVAMD) is the most common cause of uncorrectable vision loss among the elderly in developed countries. Bevacizumab and ranibizumab are the most frequently used anti-vascular endothelial growth factor (VEGF) agents injected intravitreally to treat NVAMD.

METHODS: For this systematic review, we included only randomized controlled trials in which the 2 anti-VEGF agents had been compared directly. The primary outcome was 1-year gain in best-corrected visual acuity (BCVA) of ≥15 letters. We followed Cochrane methods for trial selection, data extraction, and data analyses. Relative effects of bevacizumab versus ranibizumab are presented as estimated risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs).

RESULTS: We identified 6 eligible randomized controlled trials with 2809 participants. The proportion of eyes that gained ≥15 letters of BCVA by 1 year was similar for the 2 agents when the same regimens were compared (RR, 0.90; 95% CI, 0.73-1.11). The mean change in BCVA from baseline also was similar (MD, -0.5 letter; 95% CI, -1.6 to +0.6). Other BCVA and quality of life outcomes were similar for the 2 agents. One -year treatment cost with ranibizumab was 5.1 and 25.5 times the cost for bevacizumab in the 2 largest trials. Ocular adverse events were uncommon (<1%), and rates were similar for the 2 agents.

CONCLUSIONS: We found no important difference in effectiveness or safety between bevacizumab and ranibizumab for NVAMD treatment, but there was a large cost difference.

PMID: 26477843 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Oct 15. [Epub ahead of print]

Ranibizumab or Bevacizumab for Neovascular Age-Related Macular Degeneration According to the Lucentis Compared to Avastin Study Treat-and-Extend Protocol: Two-Year Results.

Berg K, Hadzalic E, Gjertsen I, Forsaa V, Berger LH, Kinge B, Henschien H, Fossen K, Markovic S, Pedersen TR, Sandvik L, Bragadóttir R.

PURPOSE: To compare the efficacy and safety of bevacizumab (Avastin; F. Hoffmann-La Roche Ltd, Basel, Switzerland) versus ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland) for neovascular age-related macular degeneration (nAMD) after 2 years when using a treat-and-extend protocol.

DESIGN: Multicenter, randomized, noninferiority trial with a noninferiority limit of 5 letters.

PARTICIPANTS: Patients 50 years of age or older with previously untreated nAMD in 1 eye and best-corrected visual acuity 20/25 to 20/320.

METHODS: Patients were assigned randomly to receive intravitreal injections with either ranibizumab 0.5 mg or bevacizumab 1.25 mg. Injections were given every 4 weeks until inactive disease was achieved. The treatment interval then was extended by 2 weeks at a time up to a maximum of 12 weeks. In the event of a recurrence, the treatment interval was shortened by 2 weeks at a time.

MAIN OUTCOME MEASURE: Mean change in visual acuity at 2 years.

RESULTS: Of a total of 441 randomized patients, 339 patients (79%) completed the 2-year visit. According to per-protocol analysis at 2 years, bevacizumab was equivalent to ranibizumab, with 7.4 and 6.6 letters gained, respectively (95% confidence interval [CI] of mean difference, -4.1 to 2.5; P = 0.634). Intention-to-treat analysis was concordant, with a gain of 7.8 letters for bevacizumab and 7.5 letters for ranibizumab (95% CI of mean difference, -3.2 to 2.7; P = 0.873). The 2-year results did not show any significant difference in mean central retinal thickness, with a decrease of -113 μm for bevacizumab and -122 μm for ranibizumab (95% CI of mean difference, -32 to 15; P = 0.476). There was a statistically significant difference between the drugs regarding the number of treatments given, with 18.2 injections for bevacizumab and 16.0 injections for ranibizumab (95% CI of mean difference, -3.4 to -1.0; P ≤ 0.001). The number of serious adverse events was similar between the groups over the course of the study.

CONCLUSIONS: At 2 years, bevacizumab and ranibizumab had an equivalent effect on visual acuity and reduction of central retinal thickness when administered according to a treat-and-extend protocol for nAMD. There was no significant difference in the number of serious adverse events between the treatment groups.

PMID: 26477842 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Oct 15. [Epub ahead of print]

Scheduled versus Pro Re Nata Dosing in the VIEW Trials.

Richard G, Monés J, Wolf S, Korobelnik JF, Guymer R, Goldstein M, Norenberg C, Sandbrink R, Zeitz O.

PURPOSE: To analyze visual acuity (VA) outcomes before and after preplanned treatment regimen change in the VIEW studies at week 52 (W52).

DESIGN: Multiple post hoc analyses for retrospectively defined subgroups in 2 multicenter, multinational, double-masked trials.

PARTICIPANTS: Two thousand four hundred fifty-seven neovascular age-related macular degeneration (AMD) patients.

METHODS: Patients were randomized to treatment with 0.5 mg ranibizumab given monthly, a 0.5-mg or 2-mg intravitreal aflibercept injection given monthly, or 2 mg intravitreal aflibercept given every other month, after 3 initial monthly doses, up to W52. From W52 through W96, patients received their original dosing assignment using a capped pro re nata (PRN) regimen, with defined retreatment criteria based on VA and morphologic signs of disease activity and mandatory dosing at least every 12 weeks.

MAIN OUTCOME MEASURES: Best-corrected VA (BCVA) and optical coherence tomography assessments were mandatory at all visits from baseline to W96. Outcomes were changes in BCVA and central retinal thickness. Outcomes were evaluated in all patients who completed 2 years of the VIEW studies using the last observation carried forward method for missing data at interim visits.

RESULTS: After W52, approximately 20% of patients lost 5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or more across all treatment arms with PRN treatment. Patients who met the retreatment criterion of loss of 5 ETDRS letters or more in the first quarter of the PRN dosing phase did not recover; mean final VA loss across the 4 study arms was -4.4 to -5.8 letters. Outcomes of these patients up to W52 were indistinguishable from those of the overall population. There were no differences between groups in serious ocular adverse events or Anti-Platelet Trialists' Collaboration arterial thromboembolic events through W96.

CONCLUSIONS: These analyses suggest that there are subgroups of patients for whom VA outcomes in the second year of the VIEW studies were less stable than in the first year and for whom W52 seems to be an important inflection point. Although alternate reasons specific to the nature of the underlying AMD cannot be fully excluded, the switch in treatment regimen at W52 is a plausible explanation.

PMID: 26477840 [PubMed - as supplied by publisher]

Vestn Oftalmol. 2015 Jul-Aug;131(4):60-5.

[Central retinal changes after ranibizumab injection for wet age-related macular degeneration]. [Article in Russian]

Bikbov MM, Fayzrakhmanov RR, Yarmukhametova AL.

AIM: to assess the dynamics of macular morphofunctional parameters in wet age-related macular degeneration after three injections of ranibizumab.

MATERIAL AND METHODS: A total of 76 patients with classic choroidal neovascular membrane were examined. The latter could be seen on optical coherence tomography scans before the treatment as an optically heterogeneous formation beneath the neurosensory epithelium. The point of fixation was located 2 -10 degrees from the fovea according to microperimetry testing. Wedge-like reduction of light sensitivity down to 0-2 dB corresponded to the area of neovascularization.

RESULTS: Macular sensitivity improved from 7.24 ± 2.73 dB to 13.88 ± 1.94 dB ($p < 0.05$) after a course of three ranibizumab injections, the most significant changes taking place after the third one. The point of fixation moved somewhat back to the fovea after each injection. Morphological parameters of neovascular membranes gradually decreased: after the first injection the height went down to 20.29 ± 17.84 µm and the width--down to 1200 ± 300 µm on average, after the second one the height was 14.39 ± 9.83 µm, width--1000 ± 175 µm, after the third one the height and the width were 13.31 ± 8.13 µm and 900 ± 100 µm correspondingly ($p < 0.05$).

CONCLUSION: Antivascular therapy reduces the pathological effect of neovascular membrane throughout the whole treatment period. The dynamics of studied parameters are characterized by an apparent response to the first injection, which indicates the advisability of further treatment.

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Other treatment & diagnosis

Cochrane Database Syst Rev. 2015 Oct 23;10:CD006537. [Epub ahead of print]

Laser treatment of drusen to prevent progression to advanced age-related macular degeneration.

Virgili G, Michelessi M, Parodi MB, Bacherini D, Evans JR.

BACKGROUND: Drusen are amorphous yellowish deposits beneath the sensory retina. People with drusen, particularly large drusen, are at higher risk of developing age-related macular degeneration (AMD). The most common complication in AMD is choroidal neovascularisation (CNV), the growth of new blood vessels in the centre of the macula. The risk of CNV is higher among people who are already affected by CNV in one eye.It has been observed clinically that laser photocoagulation of drusen leads to their disappearance and may prevent the occurrence of advanced disease (CNV or geographic atrophy) associated with visual loss.

OBJECTIVES: To examine the effectiveness and adverse effects of laser photocoagulation of drusen in AMD.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2015, Issue 7), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to August 2015), EMBASE (January 1980 to August 2015), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to August 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 3 August 2015.

SELECTION CRITERIA: Randomised controlled trials (RCTs) of laser treatment of drusen in AMD in which laser treatment had been compared with no intervention or sham treatment. Two types of trials were included. Some trials studied one eye of each participant (unilateral studies); other studies recruited participants with bilateral drusen and randomised one eye to photocoagulation or control and the fellow eye to the other group.

DATA COLLECTION AND ANALYSIS: Two review authors independently selected studies and extracted data. We pooled data from unilateral and bilateral studies using a random-effects model. For the bilateral studies, we estimated the within-person correlation coefficient from one study and assumed it was valid for the others.

MAIN RESULTS: The update of this review found two additional studies, totaling 11 studies that randomised 2159 participants (3580 eyes) and followed them up to two years, of which six studies (1454 participants) included people with one eye randomised to treatment and one to control. Studies were conducted in Australia, Europe and North America.Overall, the risk of bias in the included studies was low, particularly for the larger studies and for the primary outcome development of CNV. Photocoagulation did not reduce the development of CNV at two years' follow-up (odds ratio (OR) 1.07, 95% confidence interval (CI) 0.79 to 1.46, 11 studies, 2159 participants (3580 eyes), high quality evidence). This estimate means that, given an overall occurrence of CNV of 8.3% in the control group, we estimated an absolute risk reduction by no more than 1.4% in the laser group, according to the lower CI limit. Only two studies investigated the effect on the development of geographic atrophy and could not show a difference, but estimates were imprecise (OR 1.30, 95% CI 0.38 to 4.51, two studies, 148 participants (148 eyes), low quality evidence).Among secondary outcomes, photocoagulation led to drusen reduction (OR 9.16, 95% CI 6.28 to 13.4, three studies, 570 participants (944 eyes), high quality evidence) but was not shown to limit loss of 3 or more lines of visual acuity (OR 0.99, 95% CI 0.81 to 1.22, nine studies, 2002 participants (2386 eyes), moderate quality evidence).In a subgroup analysis, no difference could be shown for conventional visible (eight studies) versus subthreshold invisible (four studies) photocoagulation for the primary outcomes (P value = 0.29). The effect in the subthreshold group did not suggest a relevant benefit (OR 1.27, 95% CI 0.82 to 1.98). No study used micropulse subthreshold photocoagulation.No other adverse effects (apart from development of CNV, geographic atrophy or visual loss) were reported.

AUTHORS' CONCLUSIONS: The trials included in this review confirm the clinical observation that laser photocoagulation of drusen leads to their disappearance. However, treatment does not result in a reduction in the risk of developing CNV, and was not shown to limit the occurrence of geographic atrophy or visual acuity loss.Ongoing studies are being conducted to assess whether the use of extremely short laser pulses (i.e. nanosecond laser treatment) cannot only lead to drusen regression but also prevent neovascular AMD.

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Ophthalmology. 2015 Oct 17. [Epub ahead of print]

Ultrahigh-Speed, Swept-Source Optical Coherence Tomography Angiography in Nonexudative Age-Related Macular Degeneration with Geographic Atrophy.

Choi W, Moult EM, Waheed NK, Adhi M, Lee B, Lu CD, de Carlo TE, Jayaraman V, Rosenfeld PJ, Duker JS, Fujimoto JG.

PURPOSE: To investigate ultrahigh-speed, swept-source optical coherence tomography (SSOCT) angiography for visualizing vascular changes in eyes with nonexudative age-related macular degeneration (AMD) with geographic atrophy (GA).

DESIGN: Observational, prospective, cross-sectional study.

PARTICIPANTS: A total of 63 eyes from 32 normal subjects and 12 eyes from 7 patients with nonexudative AMD with GA.

METHODS: A 1050-nm, 400-kHz A-scan rate SSOCT system was used to perform volumetric optical

coherence tomography angiography (OCTA) of the retinal and choriocapillaris (CC) vasculatures in normal subjects and patients with nonexudative AMD with GA. Optical coherence tomography angiography using variable interscan time analysis (VISTA) was performed to assess CC alteration and differentiate varying degrees of CC flow impairment.

MAIN OUTCOME MEASURES: Qualitative comparison of retinal and CC vasculatures in normal subjects versus those in patients with a clinical diagnosis of nonexudative AMD with GA.

RESULTS: In all 12 eyes with GA, OCTA showed pronounced CC flow impairment within the region of GA. In 10 of the 12 eyes with GA, OCTA with VISTA showed milder CC flow impairment extending beyond the margin of GA. Of the 5 eyes exhibiting foveal-sparing GA, OCTA showed CC flow within the region of foveal sparing in 4 of the eyes.

CONCLUSIONS: The ability of ultrahigh-speed, swept-source OCTA to noninvasively visualize alterations in the retinal and CC vasculatures makes it a promising tool for assessing nonexudative AMD with GA. Optical coherence tomography angiography using VISTA can distinguish varying degrees of CC alteration and flow impairment and may be useful for elucidating disease pathogenesis, progression, and response to therapy.

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Prog Retin Eye Res. 2015 Oct 16. [Epub ahead of print]

Investigating the choriocapillaris and choroidal vasculature with new optical coherence tomography technologies.

Ferrara D, Waheed NK, Duker JS.

Abstract: The body of knowledge of in vivo investigation of the choroid has been markedly enhanced by recent technological advances in optical coherence tomography (OCT). New insights elucidating the morphological features of the choriocapillaris and choroidal vasculature, in both physiological and pathological conditions, indicate that the choroid plays a pivotal role in many posterior segment diseases. In this article, a review of the histological characteristics of the choroid, which must be considered for the proper interpretation of in vivo imaging, is followed by a comprehensive discussion of fundamental principles of the current state-of-the-art in OCT, including cross-sectional OCT, en face OCT, and OCT angiography using both spectral domain OCT and swept source OCT technologies. A detailed review of the tomographic features of the choroid in the normal eye is followed by relevant findings in prevalent chorioretinal diseases, focusing on major causes of vision loss such as typical early and advanced age-related macular degeneration, polypoidal choroidal vasculopathy, central serous chorioretinopathy, pachychoroid spectrum disorders, diabetic choroidopathy, and myopia.

PMID: 26478514 [PubMed - as supplied by publisher]

J Ophthalmol. 2015;2015:343515. Epub 2015 Sep 27.

Optical Coherence Tomography Angiography in Retinal Vascular Diseases and Choroidal Neovascularization.

Mastropasqua R, Di Antonio L, Di Staso S, Agnifili L, Di Gregorio A, Ciancaglini M, Mastropasqua L2

Purpose: To assess the ability of optical coherence tomography-angiography (OCT-A) to show and analyze retinal vascular patterns and the choroidal neovascularization (CNV) in retinal vascular diseases.

Methods: Seven eyes of seven consecutive patients with retinal vascular diseases were examined. Two healthy subjects served as controls. All eyes were scanned with the SD-OCT XR Avanti (Optovue Inc, Fremont CA, USA). Split spectrum amplitude decorrelation angiography algorithm was used to identify the

blood flow within the tissue. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) with Spectralis HRA + OCT (Heidelberg Engineering GmbH) were performed.

Results: In healthy subjects OCT-A visualized major macular vessels and detailed capillary networks around the foveal avascular zone. Patients were affected with myopic CNV (2 eyes), age-related macular degeneration related (2), branch retinal vein occlusion (BRVO) (2), and branch retinal artery occlusion (BRAO) (1). OCT-A images provided distinct vascular patterns, distinguishing perfused and nonperfused areas in BRVO and BRAO and recognizing the presence, location, and size of CNV.

Conclusions: OCT-A provides detailed images of retinal vascular plexuses and quantitative data of pathologic structures. Further studies are warranted to define the role of OCT-A in the assessment of retinovascular diseases, with respect to conventional FA and ICG-A.

PMID: 26491548 [PubMed] PMCID: PMC4600507

Clin Ophthalmol. 2015 Sep 28;9:1829-34. eCollection 2015.

Stereotactic radiotherapy for wet age-related macular degeneration: current perspectives.

Neffendorf JE, Jackson TL.

Abstract: Neovascular age-related macular degeneration is a leading cause of blindness in the developed world. Currently, the treatment of choice is intravitreal injections of anti-VEGF medications. These require frequent dosing, up to monthly, and impose a substantial burden on patients and the health economy. Ionizing radiation was proposed as a possible treatment for age-related macular degeneration due to its anti-inflammatory and anti-fibrotic properties. Stereotactic radiotherapy is an outpatient-based radiotherapy platform that provides stereotactic application of low energy X-ray to the retina in three highly collimated beams that cross the inferior sclera to overlap at the macula. A randomized, double-masked, sham-controlled trial of 230 patients (INTREPID) showed that a single dose of stereotactic radiotherapy significantly reduces the number of intravitreal anti-VEGF injections needed over 2 years. A larger randomized controlled trial (STAR) is underway.

PMID: 26491243 [PubMed] PMCID: PMC4599143

Ophthalmologica. 2015 Oct 22. [Epub ahead of print]

Retinal Pigment Epithelium Tears: Risk Factors, Mechanism and Therapeutic Monitoring.

Clemens CR, Eter N.

Abstract: Tears of the retinal pigment epithelium (RPE) are most commonly associated with vascularised RPE detachment due to age-related macular degeneration (AMD), and they usually involve a deleterious loss in visual acuity. Recent studies suggest an increase in RPE tear incidences since the introduction of anti-vascular endothelial growth factor (anti-VEGF) therapies as well as a temporal association between the tear event and the intravitreal injection. As the number of AMD patients and the number of administered anti-VEGF injections increase, both the challenge of RPE tear prevention and the treatment after RPE tear formation have become more important. At the same time, the evolution of retinal imaging has significantly contributed to a better understanding of RPE tear development in recent years. This review summarises the current knowledge on RPE tear development, predictive factors, and treatment strategies before and after RPE tear formation.

PMID: 26489018 [PubMed - as supplied by publisher]

Pathogenesis

Eye (Lond). 2015 Oct 23. [Epub ahead of print]

Complement pathway biomarkers and age-related macular degeneration.

Gemenetzi M, Lotery AJ.

Abstract: In the age-related macular degeneration (AMD) 'inflammation model', local inflammation plus complement activation contributes to the pathogenesis and progression of the disease. Multiple genetic associations have now been established correlating the risk of development or progression of AMD. Stratifying patients by their AMD genetic profile may facilitate future AMD therapeutic trials resulting in meaningful clinical trial end points with smaller sample sizes and study duration.

PMID: 26493033 [PubMed - as supplied by publisher]

Mol Ther Nucleic Acids. 2015 Oct 20;4:e258.

Novel Types of Small RNA Exhibit Sequence- and Target-dependent Angiogenesis Suppression Without Activation of Toll-like Receptor 3 in an Age-related Macular Degeneration (AMD) Mouse Model.

Takanashi M, Sudo K, Ueda S, Ohno S, Yamada Y, Osakabe Y, Goto H, Matsunaga Y, Ishikawa A, Usui Y, Kuroda M.

Abstract: RNA interference (RNAi) has become a powerful tool for suppressing gene expression in vitro and in vivo. A great deal of evidence has demonstrated the potential for the use of synthetic small interfering RNAs (siRNAs) as therapeutic agents. However, the application of siRNA to clinical medicine is still limited, mainly due to sequence-independent suppression of angiogenesis mediated by Toll-like receptor 3 (TLR3). Here, we describe novel types of synthetic RNA, named nkRNA and PnkRNA, that exhibit sequence-specific gene silencing through RNAi without activating TLRs or RIG-I-like receptor signaling. In addition, we confirmed the therapeutic effect for the novel types of RNA in an animal model of age-related macular degeneration (AMD) without retinal degeneration. These data indicate that nkRNA and PnkRNA are of great potential utility as therapies against blinding choroidal neovascularization due to AMD.

PMID: 26484944 [PubMed]

J Control Release. 2015 Oct 19. [Epub ahead of print]

Multivalent nanoparticles bind the retinal and choroidal vasculature.

Hennig R, Ohlmann A, Staffel J, Pollinger K, Haunberger A, Breunig M, Schweda F, Tamm E, Goepferich A.

Abstract: The angiotensin II receptor type 1 (AT1R), which is expressed in blood vessels of the posterior eye, is of paramount significance in the pathogenesis of severe ocular diseases such as diabetic retinopathy and age-related macular degeneration. However, small molecule angiotensin receptor blockers (ARBs) have not proven to be a significant therapeutic success. We report here on a nanoparticle system consisting of ARB molecules presented in a multivalent fashion on the surface of quantum dots (Qdots). As a result of the multivalent receptor binding, nanoparticles targeted cells with high AT1R expression and inhibited their angiotensin receptor signaling with an IC50 of 3.8nM while showing only minor association to cells with low AT1R expression. After intravenous injection into the tail vein of mice, multivalent nanoparticles accumulated in retinal and choroidal blood vessels of the posterior eye. At the same time, multivalent ligand display doubled the Qdot concentration in the blood vessels compared to non-targeted Qdots. Remarkably, ARB-targeted Qdots showed no pronounced accumulation in AT1R-expressing off-target tissues such as the kidney. Following systemic application, this multivalent targeting approach has

the potential to amplify AT1R blockade in the eye and concomitantly deliver a therapeutic payload into ocular lesions.

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A rare penetrant TIMP3 mutation confers relatively late onset choroidal neovascularisation which can mimic age-related macular degeneration.

Warwick A, Gibson J, Sood R, Lotery A.

Purpose: To perform a genotype-phenotype correlation for three patients heterozygous for a missense mutation in the tissue inhibitor of metalloproteinase 3 (TIMP3) gene.

Methods: Retrospective, observational case series. The medical records and photographs were reviewed for three patients diagnosed at the time with neovascular age-related macular degeneration (AMD). All were later found to carry a predicted C113G mutation in the TIMP3 gene, other known mutations in which are associated with Sorsby's fundus dystrophy.

Results: All three patients developed drusen and bilateral choroidal neovascularisation with subsequent disciform scarring and atrophy. Visual acuity rapidly deteriorated to <6/60 in both eyes. The age of onset varied from 56 to 64 years and the interval to contralateral eye involvement varied from 4 to 6 years. Two of the three patients had a family history of AMD. All three patients were heterozygous for the C113G nucleotide change, resulting in a Ser38Cys change at the N terminus of the TIMP3 protein.

Conclusion: This case series suggests the C113G TIMP3 variant may represent a novel highly penetrant mutation causing choroidal neovascularisation of relatively late onset for Sorsby's fundus dystrophy, mimicking early onset AMD.

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Wnt signaling in age-related macular degeneration: human macular tissue and mouse model.

Tuo J, Wang Y, Cheng R, Li Y, Chen M, Qiu F, Qian H, Shen D, Penalva R, Xu H, Ma JX, Chan CC.

BACKGROUND: The wingless-type MMTV integration site (Wnt) signaling is a group of signal transduction pathways. In canonical Wnt pathway, Wnt ligands bind to low-density lipoprotein receptor-related protein 5 or 6 (LRP5 or LRP6), resulting in phosphorylation and activation of the receptor. We hypothesize that canonical Wnt pathway plays a role in the retinal lesion of age-related macular degeneration (AMD), a leading cause of irreversible central visual loss in elderly.

METHODS: We examined LRP6 phosphorylation and Wnt signaling cascade in human retinal sections and plasma kallistatin, an endogenous inhibitor of the Wnt pathway in AMD patients and non-AMD subjects. We also used the Ccl2 (-/-) /Cx3cr1 (-/-) /rd8 and Ccl2 (-/-) /Cx3cr1 (gfp/gfp) mouse models with AMD-like retinal degeneration to further explore the involvement of Wnt signaling activation in the retinal lesions in those models and to preclinically evaluate the role of Wnt signaling suppression as a potential therapeutic option for AMD.

RESULTS: We found higher levels of LRP6 (a key Wnt signaling receptor) protein phosphorylation and transcripts of the Wnt pathway-targeted genes, as well as higher beta-catenin protein in AMD macula compared to controls. Kallistatin was decreased in the plasma of AMD patients. Retinal non-phosphorylated -β-catenin and phosphorylated-LRP6 were higher in Ccl2 (-/-) /Cx3cr1 (-/-) /rd8 mice than that in wild type. Intravitreal administration of an anti-LRP6 antibody slowed the progression of retinal lesions in Ccl2 (-/-) /

Cx3cr1 (-/-) /rd8 and Ccl2 (-/-) /Cx3cr1 (gfp/gfp) mice. Electroretinography of treated eyes exhibited larger amplitudes compared to controls in both mouse models. A2E, a retinoid byproduct associated with AMD was lower in the treated eyes of Ccl2 (-/-) /Cx3cr1 (-/-) /rd8 mice. Anti-LRP6 also suppressed the expression of Tnf-α and Icam-1 in Ccl2 (-/-) /Cx3cr1 (-/-) /rd8 retinas.

CONCLUSIONS: Wnt signaling may be disturbed in AMD patients, which could contribute to the retinal inflammation and increased A2E levels found in AMD. Aberrant activation of canonical Wnt signaling might also contribute to the focal retinal degenerative lesions of mouse models with Ccl2 and Cx3cr1 deficiency, and intravitreal administration of anti-LRP6 antibody could be beneficial by deactivating the canonical Wnt pathway.

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[Role of infection in the pathogenesis of age-related macular degeneration]. [Article in Russian]

Slepova OS, Eremeeva EA, Ryabina MV, Sorozhkina ES.

AIM: to study the role of infectious agents in the development and progression of AMD by means of serodiagnostic assay for a complex of ophthalmotropic and opportunistic infections.

MATERIAL AND METHODS: The study enrolled 61 patients (23 men, 38 women) aged 43-68 years and diagnosed in accordance with AREDS classification of AMD. Serodiagnostic tests were performed for 11 infections with the purpose of identifying antigen-specific antibodies in the serum.

RESULTS: Activation markers of one or several infections were detected in most of the patients with AMD.

CONCLUSION: Herpes viruses (HSV1 and CMV) along with some opportunistic pathogens are important factors in the pathogenesis of AMD, thereby, specific treatment should be performed in these patients.

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Diet, lifestyle & low vision

Am J Clin Nutr. 2015 Oct 21. [Epub ahead of print]

Adherence to a Mediterranean diet, genetic susceptibility, and progression to advanced macular degeneration: a prospective cohort study.

Merle BM, Silver RE, Rosner B, Seddon JM.

BACKGROUND: Adherence to a Mediterranean-type diet is linked to a lower risk of mortality and chronic disease, but the association with the progression of age-related macular degeneration (AMD) and genetic susceptibility is unknown.

OBJECTIVE: We examined the association of adherence to the Mediterranean diet and genetic susceptibility with progression to advanced AMD.

DESIGN: Among 2525 subjects in the AREDS (Age-Related Eye Disease Study), 1028 eyes progressed to advanced AMD over 13 y. Baseline data for demographic and behavioral covariates were collected by using questionnaires. Dietary data were collected from food-frequency questionnaires. The alternate Mediterranean diet (aMeDi) score (range: 0-9) was constructed from individual intakes of vegetables, fruit, legumes, whole grains, nuts, fish, red and processed meats, alcohol, and the ratio of monounsaturated to saturated fats. Ten genetic loci in 7 genes [complement factor H (CFH), age-related maculopathy susceptibility 2/high-temperature requirement A serine peptidase 1 (ARMS2/HTRA1), complement component 2 (C2), complement factor B (CFB), complement component 3 (C3), collagen type VIII α 1 (COL8A1), and RAD51 paralog B (RAD51B)] were examined. Survival analysis was used to assess

individual eyes for associations between incident AMD and aMeDi score, as well as interaction effects between aMeDi score and genetic variation on risk of AMD.

RESULTS: A high aMeDi score (score of 6-9) was significantly associated with a reduced risk of progression to advanced AMD after adjustment for demographic, behavioral, ocular, and genetic covariates (HR: 0.74; 95% CI: 0.61, 0.91; P-trend = 0.007). The aMeDi score was significantly associated with a lower risk of incident advanced AMD among subjects carrying the CFH Y402H nonrisk (T) allele (P-trend = 0.0004, P-interaction = 0.04). The aMeDi score was not associated with AMD among subjects who were homozygous for the risk (C) allele.

CONCLUSION: Higher adherence to a Mediterranean diet was associated with reduced risk of progression to advanced AMD, which may be modified by genetic susceptibility.

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Variation in carotenoid content of kale and other vegetables: a review of pre and post-harvest effects.

Walsh R, Bartlett H, Eperjesi F.

Abstract: Lutein and zeaxanthin are carotenoids that are selectively taken up into the macula of the eye where they are thought to protect against the development of age-related macular degeneration. They are obtained from dietary sources, with the highest concentrations being found in dark green leafy vegetables, such as kale, and spinach. In this review, compositional variation due to variety/cultivar, stage of maturity, climate or season, farming practice, storage and processing effects are highlighted. Only data from studies which report on lutein and zeaxanthin content in foods are reported. The main focus is kale, however other predominantly xanthophyll containing vegetables such as spinach and broccoli are included. A small amount of data about exotic fruits is also referenced for comparison. The qualitative and quantitative composition of carotenoids in fruits and vegetables is known to vary with multiple factors. In kale, lutein and zeaxanthin levels are affected by pre harvest effects such as maturity, climate and farming practice. Further research is needed to determine the post-harvest processing and storage effects of lutein and zeaxanthin in kale; this will enable precise suggestions for increasing retinal levels of these nutrients.

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Impact of age-related macular degeneration in patients with glaucoma: understanding the patients' perspective.

Skalicky SE, Fenwick E, Martin KR, Crowston J, Goldberg I, McCluskey P.

BACKGROUND: To measure the impact of age-related macular degeneration on vision-related activity limitation and preference-based status for glaucoma patients.

DESIGN: Cross-sectional study.

PARTICIPANTS: 200 glaucoma patients of whom 73 had age-related macular degeneration.

METHODS: Sociodemographic information, visual field parameters and visual acuity were collected. Age-related macular degeneration was scored using the Age Related Eye Disease Study system.

MAIN OUTCOME MEASURES: The Rasch-analysed Glaucoma Activity Limitation-9 and the Visual Function Questionnaire Utility Index measured vision-related activity limitation and preference-based status, respectively. Regression models determined factors predictive of vision-related activity limitation and

preference-based status. Differential item functioning compared Glaucoma Activity Limitation-9 item difficulty for those with and without age-related macular degeneration.

RESULTS: Mean age was 73.7 (±10.1) years. Lower better-eye mean deviation (β: 1.42, 95% confidence interval: 1.24-1.63, $p < 0.001$) and age-related macular degeneration (β: 1.26 95% confidence interval: 1.10-1.44, $p = 0.001$) were independently associated with worse vision-related activity limitation. Worse eye visual acuity (β: 0.978, 95% confidence interval: 0.961-0.996, $p = 0.018$), high risk age-related macular degeneration (β: 0.981, 95% confidence interval: 0.965-0.998, $p = 0.028$) and severe glaucoma (β: 0.982, 95% confidence interval: 0.966-0.998, $p = 0.032$) were independently associated with worse preference-based status. Glaucoma patients with age-related macular degeneration found using stairs, walking on uneven ground and judging distances of foot to step/curb significantly more difficult than those without age-related macular degeneration.

CONCLUSIONS: Vision-related activity limitation and preference-based status are negatively impacted by severe glaucoma and age-related macular degeneration. Patients with both conditions perceive increased difficulty walking safely compared to patients with glaucoma alone.

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