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Drug Treatment

Ophthalmology. 2012 Jul 17. [Epub ahead of print]

Improved Vision-Related Function after Ranibizumab for Macular Edema after Retinal Vein Occlusion: Results from the BRAVO and CRUISE Trials.

Varma R, Bressler NM, Suñer I, Lee P, Dolan CM, Ward J, Colman S, Rubio RG; BRAVO and CRUISE Study Groups.

Doheny Eye Institute, University of Southern California, Los Angeles, California.

PURPOSE: To examine the impact of intravitreal ranibizumab on patient-reported visual function using the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) through 6 months in patients with macular edema (ME) secondary to branch or central retinal vein occlusion (RVO).

DESIGN: Two multicenter, double-masked trials, which enrolled participants with ME secondary to branch or central RVO: the RanibizumaB for the Treatment of Macular Edema following BRAnch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) trial or the Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety (CRUISE) trial.

PARTICIPANTS: Three hundred ninety-seven BRAVO and 392 CRUISE patients.

METHODS: Patients were randomized 1:1:1 to monthly sham, 0.3-mg, or 0.5-mg injections of ranibizumab for 6 months.

MAIN OUTCOME MEASURES: Although visual acuity was the main outcome measure for the trials, mean change from baseline in NEI VFQ-25 scores at month 6 was a secondary outcome measure.

RESULTS: In BRAVO, among the 132, 134, and 131 patients randomized, respectively, to sham, 0.3 mg ranibizumab, or 0.5 mg ranibizumab, the study eye was the worse-seeing eye in 121 (91.7%), 118 (88.1%), and 125 (95.4%) patients and 123 (93.2%), 128 (95.5%), and 125 (95.4%), respectively, had a 6-month follow-up visit. In CRUISE, among the 130, 132, and 130 patients randomized, respectively, to sham, 0.3 mg ranibizumab, and 0.5 mg ranibizumab, the study eye was the worse-seeing eye in 117 (90.0%), 123 (93.2%), and 120 (92.3%) patients and 115 (88.5%), 129 (97.7%), and 119 (91.5%), respectively, had a 6-month follow-up visit. In both trials, patients treated with ranibizumab reported greater mean improvements in visual function, with substantial differences observed as early as month 1, including the NEI VFQ-25 composite score and near and distance activities subscales, compared with sham patients. P values for comparisons with sham for the composite score and these 2 subscales were <0.05.

CONCLUSIONS: These results from the BRAVO and CRUISE trials indicate that patients with ME from

RVOs treated with monthly ranibizumab report greater improvements in vision-related function compared with sham-treated patients through 6 months, even when a majority of patients present with RVOs in the worse-seeing eye.

PMID: 22817833 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2012 Jul 23. [Epub ahead of print]

[Efficacy of prophylactic treatment of intraocular pressure spikes due to intravitreal injections.] [Article in French]

El Chehab H, Le Corre A, Giraud JM, Ract-Madoux G, Swalduz B, Dot C.

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PURPOSE: The purpose of this study was to evaluate intraocular pressure increase after intravitreal injections (IVIs) and the effect of prophylactic pressure-lowering medications.

METHODS: A prospective study of 210 anti-vascular endothelial growth factor (VEGF) IVI (0.05mL of bevacizumab or ranibizumab), that were divided into five groups, group 1: no intraocular pressure (IOP)-lowering medication (n=50); group 2: apraclonidine 1 % one drop 2hours prior to IVI (n=50); group 3: acetazolamide 250mg 2hours prior (n=50); group 4: fixed combination brimonidine+timolol (n=30); group 5: fixed combination dorzolamide+timolol (n=30). IOP was measured before, immediately after (T1), 15min after (T15) and 45min after (T45) the IVI using a Perkins tonometer.

RESULTS: The mean IOP peak in group 1 was 46.4±4.8mmHg at T1, 21.7±5.7mmHg at T15 and 15.4±4.3mmHg at T45. Apraclonidine 1 % and the fixed combinations produced a significant reduction of IOP at every time point, of around 9mmHg at T1. The reduction in IOP obtained with acetazolamide was not significant versus group 1 at T1 (-1.6mmHg, P=0.12), but became significant at T15 and T45 (respectively, P=0.011 and P=0.015).

CONCLUSIONS: IOP spikes are high but transient following IVI. Acetazolamide proved to be ineffective in preventing this spike. Topical medications, however, produced a significant reduction in IOP spike as well as in the duration of the increased pressure, with no significant difference between fixed combinations and 1 % apraclonidine at T1. It would seem advisable to prevent this IOP spike in the case of repeated injections, particularly in patients with glaucoma.

PMID: 22832030 [PubMed - as supplied by publisher]

Clin Exp Optom. 2012 Jul 26. doi: 10.1111/j.1444-0938.2012.00766.x. [Epub ahead of print]

Retinal angiomatous proliferation responds safely to a double dose (1.0 mg) of ranibizumab.

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Abstract

A 77-year-old man presented with sudden foggy central vision in the right eye. The visual acuity (VA) was 6/60 (R) and 6/6 (L). Funduscopy revealed superficial macular haemorrhage in the right eye. Using fluorescein angiography and indocyanine green angiography, retinal angiomatous proliferation was confirmed. Two intra-vitreal injections of bevacizumab were given but the VA did not improve. Following this, he received an intra-vitreal injection of ranibizumab. Regression of the retinal angiomatous proliferation was observed and the VA of the right eye returned to 6/10. Simultaneously, his left eye suffered from

sudden visual loss and retinal angiomatous proliferation was diagnosed. Three intra-vitreal injections of ranibizumab were given. Regression of the retinal angiomatous proliferation was observed and the VA of the left eye was stabilised. Another 80-year-old man complained of sudden distorted vision in his left eye. Funduscopy and optical coherence tomography (OCT) revealed superficial macular haemorrhage and retinal pigment epithelial detachment (RPED). The VA was 6/12 and retinal angiomatous proliferation was diagnosed. He received an intra-vitreous injection of bevacizumab followed by photodynamic therapy (PDT). The RPED was resolved; however, the VA dropped to 2/60. Optical coherent tomography, fluorescein angiography and indocyanine green angiography were used to indentify retinal angiomatous proliferation. Intra-vitreal injection(s) of a double dose (1 mg) of ranibizumab is a worthwhile treatment, as it can stabilise and even improve the VA without significant side effects.

PMID: 22830523 [PubMed - as supplied by publisher]

Retina. 2012 Jul 19. [Epub ahead of print]

INTRAVITREAL BEVACIZUMAB TREATMENT FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION WITH GOOD VISUAL ACUITY.

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PURPOSE: To investigate the effect of intravitreal bevacizumab on the visual and anatomic outcome of patients with exudative age-related macular degeneration presenting with good visual acuity (VA).

METHODS: A file review was performed for all consecutive patients with newly diagnosed exudative age-related macular degeneration and initial VA of ≥20/40 treated in 2005 to 2010 and followed for at least 6 months. Treatment consisted of 3 loading doses of intravitreal bevacizumab every 6 weeks and was repeated when fluid or hemorrhage was present.

RESULTS: The cohort included 130 patients (150 eyes). Mean follow-up was 20.2 ± 13.2 months, and mean number of injections was 11.3 ± 6.2. At the last examination, VA was stable or improved in 106 eyes (70.7%); 11 eyes (7.3%) lost ≥3 lines. Mean logarithm of the minimum angle of resolution VA measured 0.22 ± 0.1 (0-0.3) at presentation and 0.22 ± 0.2 (0-1.3) at the last visit. Corresponding values for central macular thickness were 267 ± 75 μm (137-562) and 226 ± 75 μm (75-568) (P = 0.14). The most frequent complication (18 eyes, 12%) was corneal epithelial defects.

CONCLUSION: Prompt intravitreal bevacizumab treatment for newly diagnosed exudative age-related macular degeneration in patients with good initial best-corrected visual acuity is associated with sustained or improved vision and a good safety profile. Attempts should be made to expedite the access of these patients to treatment, regardless of initial VA.

PMID: 22825407 [PubMed - as supplied by publisher]

Indian J Ophthalmol. 2012 Jul;60(4):263-6.

Ranibizumab as an adjunct to laser for macular edema secondary to branch retinal vein occlusion.

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Abstract

Purpose: To compare the safety, efficacy, and dosing regimen of intravitreal ranibizumab as an adjunct to laser therapy for the treatment of macular edema secondary to branch retinal vein occlusion (BRVO). Materials and Methods: Thirty eyes of 30 patients of BRVO of at least 6 weeks duration were randomized into three groups: Group 1 received grid laser treatment alone, Group 2 received a single dose of intravitreal injection of ranibizumab (0.5 mg / 0.05 ml) followed by grid laser treatment on 7 th day following injection, while Group 3 received three loading doses of intravitreal ranibizumab at monthly interval (i.e. 0, 1, & 2 months) + standard laser treatment 7 days after the 1 st injection. Outcome measure noted at 6 months follow-up were the improvement in best-corrected visual acuity (BCVA) and central macular thickness (CMT). Results: At 6 months follow-up, there was an average gain of 12 letters (P=0.05), 17.5 letters (P=0.05) and 19 letters (P=0.05) in groups 1, 2, and 3, respectively, with the decrease in CMT being 208.7 µm (P=0.05), 312.9 µm (P= 0.05) and 326.8 µm (P=0.05), respectively, in these groups. Gain in BCVA of more than 3 lines was noted in 1/10 patients in Group 1(10%) as compared to 3/10 (30%) and 4/10 (40%) patients in groups 2 and 3, respectively. Conclusion: The gain in BCVA and reduction in CMT were better with combination therapy (single- and triple- dose regimen) compared to grid laser alone. Single dose of intravitreal ranibizumab with grid laser seems to be an effective therapy.

PMID: 22824593 [PubMed - in process]

Ophthalmology. 2012 Jul 19. [Epub ahead of print]

Bevacizumab for Neovascular Age-Related Macular Degeneration in China.

Li X, Hu Y, Sun X, Zhang J, Zhang M; Neovascular Age-Related Macular Degeneration Treatment Trial Using Bevacizumab Study Group.

Department of Ophthalmology, People's Hospital, Peking University, Beijing, China, and Key Laboratory of Vision Loss and Restoration, Ministry of Education, Beijing, China.

OBJECTIVE: To evaluate 2 different dosing regimens of intravitreal bevacizumab for the treatment of neovascular age-related macular degeneration (AMD) patients in China.

DESIGN: Multicenter, randomized, prospective, open-label clinical trial.

PARTICIPANTS: One hundred eighty-five patients with active neovascular AMD, exclusion of a macular scar, choroidal neovascularization not resulting from AMD, and polypoidal choroidal vasculopathy.

INTERVENTION: Patients were assigned randomly to receive intravitreal injections of bevacizumab every 6 weeks for the first 3 injections followed by injections every 6 weeks (regimen A, n = 91) or every 12 weeks (regimen B, n = 94).

MAIN OUTCOME MEASURES: The primary outcome measure was a comparison of the mean change in visual acuity from baseline. The secondary outcome measure was a comparison of the proportion of patients with a change in visual acuity of 15 letters or more. Adverse events were monitored.

RESULTS: One-hundred eighty five patients were enrolled. At 48 weeks, the increase in the mean visual acuity measurements from baseline were 12.58 letters in regimen A and 10.06 letters in regimen B (P = 0.288). At 48 weeks, the percentage of eyes losing fewer than 15 letters was 96.2% in regimen A and 93.9% in regimen B (P = 0.720). At 48 weeks, the median decrease in central retinal thickness measurements from baseline was 119 µm in regimen A and 60 µm in regimen B (P = 0.221). Adverse events during the 48 weeks included anterior chamber inflammation in 17 patients (18.7%) from regimen A and 9 patients (9.6%) from regimen B (P = 0.075). There were no other notable ocular adverse events in either group.

CONCLUSIONS: Intravitreal bevacizumab improved visual acuity and decreased macular thickness in patients with neovascular AMD when dosed either every 6 weeks or every 12 weeks after 3 doses given at 6-week intervals. Although there were no statistically significant differences between the 2 regimens, the

results tended to favor the group dosed every 6 weeks (regimen A).

PMID: 22818896 [PubMed - as supplied by publisher]

Ophthalmologe. 2012 Jul 26. [Epub ahead of print]

[Therapy of myopic choroidal neovascularization.] [Article in German]

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Abstract

Recently published studies have shown that myopic choroidal neovascularization (mCNV) is efficiently treated by anti-vascular endothelial growth factor (VEGF) drugs. Within a prospective executive study, photodynamic therapy failed to prove a significant difference over the duration of 2 years. Although a systematic evaluation of different retreatment algorithms still has to be done the administration of single injections depending on specialist assessment of morphological changes, predominantly spectral domain optical coherence tomography (SD-OCT) and fundus, has achieved a marked visual improvement. The experience of treating age-related macular degeneration should not be simply transferred to mCNV and an individual approach, not only for female patients of childbearing age, is necessary.

PMID: 22828745 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2012 Jul 24. [Epub ahead of print]

PERIPHERAL POLYPOIDAL CHOROIDAL VASCULOPATHY AS A CAUSE OF PERIPHERAL EXUDATIVE HEMORRHAGIC CHORIORETINOPATHY : A Report of 10 Eyes.

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PURPOSE: Polypoidal choroidal vasculopathy (PCV) is characterized by polyp-like sub-retinal pigment epithelium vascular abnormalities predominantly found in the macula and peripapillary region. Less commonly, PCV can be found peripherally and be a cause of peripheral exudative hemorrhagic chorioretinopathy (PEHCR). We sought to further describe the clinical spectrum of this ill-defined subgroup of PEHCR.

METHODS: A retrospective observational case series, of 10 eyes of 8 patients diagnosed with PEHCR caused by peripheral PCV, was conducted. In all cases, the presence of PCV was confirmed with indocyanine green angiography and/or fluorescein angiography and optical coherence tomography. The clinical presentation, natural history, and clinical outcomes with or without intervention were studied.

RESULTS: Patients with PEHCR caused by peripheral PCV were most commonly men, white, asymptomatic, and had a concomitant diagnosis of age-related macular degeneration. The mean age was 70 years (range, 59-82 years) with a mean follow-up of 32.5 months (range, 4-91 months). Four patients had unilateral involvement with minimal subretinal hemorrhage that resolved spontaneously, one patient

had unilateral involvement outside the macula that responded to anti-vascular endothelial growth factor therapy, one patient had unilateral involvement with subretinal hemorrhage threatening the macula that responded to anti-vascular endothelial growth factor therapy, and two patients had extensive bilateral subretinal hemorrhage requiring surgical intervention. Both patients with multiple lesions in one eye had bilateral lesions (two of eight patients). Lesions were most commonly located in the temporal periphery (8 of 10 eyes).

CONCLUSION: A new subclassification is proposed that includes both eyes with polyps and those without polyps within the spectrum of disease described previously as PEHCR. Within the spectrum of disease described previously as PEHCR exists a subgroup of lesions caused by peripheral PCV, which has not been well defined before this report. The largest case series to date of eyes with PEHCR due to peripheral PCV, a unique form of type 1 neovascularization, is further classified and described. These eyes have a spectrum of disease, including small, medium-sized, and large lesions. Although most eyes with PEHCR from peripheral PCV experience a benign course with spontaneous resolution, a subset of eyes may experience macula-threatening hemorrhage, requiring treatment with laser-based therapies, anti-vascular endothelial growth factor injections, or surgical intervention.

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Am J Ophthalmol. 2012 Jul 17. [Epub ahead of print]

Intraocular Pharmacokinetics of Ranibizumab Following a Single Intravitreal Injection in Humans.

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PURPOSE: To investigate intraocular concentrations and pharmacokinetics of ranibizumab after a single intravitreal injection in humans.

DESIGN: Prospective, noncomparative, interventional case series.

METHODS: We included 18 nonvitrectomized eyes of 18 patients (age range, 61-85 years) that were diagnosed with both clinically significant cataract and macular edema secondary to either exudative age-related macular degeneration, diabetic maculopathy, or retinal vein occlusion. Each eye received a single intravitreal injection of 0.5 mg ranibizumab. An aqueous humor sample was obtained during cataract surgery between 1 and 37 days after injection. Concentrations of unbound ranibizumab in these samples were quantified by enzyme-linked immunosorbent assay.

RESULTS: Ranibizumab concentration in aqueous humor peaked the first day after injection (range, 36.9-66.1 μg/mL) and subsequently declined in a mono-exponential fashion. Nonlinear regression analysis determined an initial peak concentration (c(max)) of 56.1 μg/mL and an elimination half-life (t(1/2)) of 7.19 days with a coefficient of determination (R(2)) of 0.90. Correction of ranibizumab concentrations for ocular volume as calculated from axial length measurements did not alter regression analysis results significantly (t(1/2), 7.15 days; R(2), 0.89).

CONCLUSIONS: In human nonvitrectomized eyes, the aqueous half-life of 0.5 mg intravitreally injected ranibizumab is 7.19 days, slightly shorter than the half-life of 9.82 days previously determined for bevacizumab by comparable methods.

PMID: 22818800 [PubMed - as supplied by publisher]

Comput Methods Programs Biomed. 2012 Jul 17. [Epub ahead of print]

Accurate detection of blood vessels improves the detection of exudates in color fundus images.

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Abstract

Exudates are one of the earliest and most prevalent symptoms of diseases leading to blindness such as diabetic retinopathy and macular degeneration. Certain areas of the retina with such conditions are to be photocoagulated by laser to stop the disease progress and prevent blindness. Outlining these areas is dependent on outlining the lesions and the anatomic structures of the retina. In this paper, we provide a new method for the detection of blood vessels that improves the detection of exudates in fundus photographs. The method starts with an edge detection algorithm which results in a over segmented image. Then the new feature-based algorithm can be used to accurately detect the blood vessels. This algorithm considers the characteristics of a retinal blood vessel such as its width range, intensities and orientations for the purpose of selective segmentation. Because of its bulb shape and its color similarity with exudates, the optic disc can be detected using the common Hough transform technique. The extracted blood vessel tree and optic disc could be subtracted from the over segmented image to get an initial estimate of exudates. The final estimation of exudates can then be obtained by morphological reconstruction based on the appearance of exudates. This method is shown to be promising since it increases the sensitivity and specificity of exudates detection to 80% and 100% respectively.

PMID: 22818584 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2012 Jul 23. [Epub ahead of print]

Fundus autofluorescence and spectral-domain optical coherence tomography findings suggesting tissue remodelling in retinal pigment epithelium tear.

Caramoy A, Fauser S, Kirchhof B.

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AIM: To study tissue remodelling and wound healing after retinal pigment epithelium (RPE) tears due to age-related macular degeneration.

METHODS: Retrospective longitudinal study of 36 eyes (33 patients) with RPE tears. Imaging was performed using fundus autofluorescence (FAF) (λ=488 nm) and spectral-domain optical coherence tomography (SD-OCT). Presence of intraretinal hyper-reflective dots in SD-OCT, which correlated with hyperfluorescent dots in FAF, indicating RPE migration was studied. Morphology of subretinal mass and RPE layer integrity in the RPE denuded area over time were examined.

RESULTS: 7 of 36 eyes (19.4%) showed patchy or hazy hyperfluorescent areas in FAF, and the majority of eyes (83.3%) showed hyper-reflective dots, which possibly represent intraretinal RPE migration and hard exudates. Homogenous subretinal mass was encountered in about half of all cases. In one case (2.8%), the RPE layer proliferated and covered the defect.

CONCLUSIONS: SD-OCT and FAF showed a considerable amount of RPE proliferation, migration and repopulation. Intraretinal RPE migration did not form a functional RPE layer. A small defect might be repaired by cell proliferation. But this RPE proliferation is not sufficient to cover large defects.

PMID: 22826551 [PubMed - as supplied by publisher]

Clin Exp Optom. 2012 Jul 23. doi: 10.1111/j.1444-0938.2012.00783.x. [Epub ahead of print]

Electronic restoration of vision in those with photoreceptor degenerations.

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Abstract

Complete loss of vision is one of the most feared sequelae of retinal disease. Currently, there are few if any treatment options available to patients that may slow or prevent blindness in diseases caused by photoreceptor loss, such as retinitis pigmentosa and age-related macular degeneration. Electronic restoration of vision has emerged over recent years as a safe and viable option for those who have lost substantial numbers of photoreceptors and who are severely vision impaired. Indeed, there has been a dramatic increase in our understanding of what is required to restore vision using an electronic retinal prosthesis. Recent reports show that for some patients, restoration of vision to the point of reading large letters is possible. In this review, we examine the types of implants currently under investigation and the results these devices have achieved clinically. We then consider a range of engineering and biological factors that may need to be considered to improve the visual performance of newer-generation devices. With added research, it is hoped that the level of vision achieved with newer generation devices will steadily improve, resulting in enhanced quality of life for those with severe vision impairment.

PMID: 22823954 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging. 2012 Jul 19:1-8. doi: 10.3928/15428877-20120712-02. [Epub ahead of print]

Noninvasive Imaging of Mitochondrial Dysfunction in Dry Age-Related Macular Degeneration.

Field MG, Comer GM, Kawaji T, Petty HR, Elner VM.

BACKGROUND AND OBJECTIVE: Oxidative stress and mitochondrial dysfunction are implicated in the pathogenesis of age-related macular degeneration (AMD). Because increased flavoprotein fluorescence (FPF) is indicative of mitochondrial dysfunction, the authors attempted to detect mitochondrial dysfunction in eyes with AMD using FPF.

PATIENTS AND METHODS: Six nonexudative eyes with AMD, including three with geographic atrophy (GA), and age-matched control eyes were imaged with a FPF device. Qualitative and quantitative analyses were conducted on the FPF images.

RESULTS: Five eyes with AMD, including all three eyes with GA, showed qualitative and/or quantitative FPF heterogeneity that was not present in control eyes. Mean FPF average intensities of eyes with AMD with ($P = .044$) and without ($P = .00060$) GA were significantly greater than those of control eyes. The standard deviations of FPF images were greater in eyes with AMD ($P = .020$).

CONCLUSION: In this small cluster of patients with AMD, retinal FPF is increased, suggesting elevated mitochondrial dysfunction. FPF heterogeneity indicates that an increased variability in mitochondrial dysfunction seems to be present in eyes with advanced disease.

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Invest Ophthalmol Vis Sci. 2012 Jul 26. [Epub ahead of print]

Behaviour of SD-OCT detected hyperreflective foci in the retina of Anti-VEGF treated patients with Diabetic Macular Edema.

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Purpose: Hyperreflective foci (HF) are observable within the neurosensory retina in diabetic macular edema (DME) using spectral domain optical coherence tomography (SD-OCT). The HF behaviour was evaluated during Anti-VEGF therapy in DME.

Methods: Fifty-one patients (mean age: 67 years) underwent SD-OCT (Heidelberg engineering, Germany) before and one month after one Anti-VEGF injection (Ranibizumab: n=30; Bevacizumab: n=21). The amount of HFs were semi-quantitatively counted, assigned to 3 groups (A: SDPs n=1-10; B: n=11-20; C: n>20) and correlated to the course of visual acuity and foveal thickness (paired t-test). Additionally the baseline HbA1c was categorized and correlated to baseline SDPs (Spearman Rho).

Results: In all eyes HFs of various amounts were detected in the foveal and parafoveal area. Foveal thickness reduced from 445.5 to 373.9µm (p=0.000) and visual acuity increased from 62.0 to 66.0 ETDRS letters (p=0.003). Regarding to the 3 HF-groups a reduction was observed in 43.1% (stable: 54.9%, more: 2.0%). This reflects a HF distribution change from 31.4% to 62.7% (Group A), from 45.1% to 31.4% (Group B) and from 23.5% to 5.9% (Group C). The HbA1c correlated significantly to the overall HF amount at baseline (0.880; p=0.000); however, no distinct overall correlation was found between the HF reduction and the course of visual acuity or retinal thickness. Only in cases of complete edema resolution (25%) HFs reduced significantly (p=0.008).

Conclusions: HFs are frequently found in DME and reduce under Anti-VEGF therapy, especially in cases of complete edema resolution; however, no distinct correlation with visual acuity was noticed. Interestingly, the baseline HF amount seems to correlate positively with HbA1c values indicating the severity of disease.

PMID: 22836760 [PubMed - as supplied by publisher]

J Nutr Health Aging. 2012;16(7):599-600.

Editorial: implementing frailty into clinical practice: we cannot wait.

Vellas B, Cestac P, Moley JE.

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Abstract

Geriatric medicine was implemented in many countries in the 1980s due to the discharge of many older adults with multiple pathologies, cognitive impairment and severe disabilities to emergency departments. In fact, at that time nobody was capable or wanted to care about these older adults with severe disabilities. For these reasons, most of the departments of geriatrics were created at that time. Most were based in sub-acute and long term care to take care of these patients. Since then, geriatric medicine has grown in many countries and now there are acute care units, day hospitals, mobile teams and memory clinics worldwide. However, today in most of these centers geriatric physicians are dealing with patients with already severe disabilities at a stage which is often not reversible. Almost 95% of the geriatric force is involved in care for already dependent older adults. We need, of course, to continue to take care of these individuals with severe disabilities, but moreover, we need to take care of the pre-frail and frail older adults. It is an absolute necessity if we want to prevent rapid disability in our aging population, and if we want to anticipate it to

promote more efficient care. Pre-frail and frail older adults are those following the Fried criteria who have a sedentary life, an involuntary weight loss, low physical activity, exhaustion, low strength. If they have one of the Fried criteria, they are pre-frail; if they have 3 or more, they are frail. Frail older adults are more likely to become dependent, but today they are not really taken into consideration by our health care systems. We need, in collaboration with the family physicians, to take up this challenge. To do it we need a targeted, strong and sustained intervention. - Targeting the pre-frail and frail older adults. To do this we need a simple tool to be used by family practitioner and other health professionals to screen those at risk of being frail. The IANA tool (a simple 5 questions) recently validated by Morley et al. is a good example. Another example is the tool used in the Gerontopole Frailty Clinics. It is useful to keep the subjective assessment of the physician if we want to keep him/her involved in the interventional process. - Important Intervention: To have a real impact the intervention must be strong. To do this a complete geriatric assessment of the pre-frail and frail patients is necessary to be able to diagnose some age-related disease at a pro-dromal stage, where it is still possible to cure the patient: e.g., early stage of macular degeneration, glaucoma, hearing impairment, mild cognitive impairment, sarcopenia (8.9) or loss of mobility. It is also an opportunity to have this population benefit from new drug trials in prodromal Alzheimer's disease in an early stage of sarcopenia for example. The evaluation must use specific tools to do most accurate diagnosis of potential age related diseases. This assessment must include also social, health, economic and psychosocial assessment, as well as the evaluation of the deficit accumulation. - A sustained Intervention. Because the aging of this population will still increase, we need to have long-term and sustained intervention. Physical exercise, cognitive exercise, nutrition intervention, social services will be needed in association of the detection and treatment of age related diseases. A recent study showed that even in older frail persons with hip fracture, a sustained resistance exercise program for one year can improve outcomes. More standardization of these multi-domain interventions is an important domain for further research. We need to find a compromise between very strong interventions which will be accepted by few frail older adults and too light interventions usually not strong enough to have a real impact. - The I.A.G.G. (International Association of Gerontology and Geriatrics), http://www.iagg.info/ and the G.A.R.N. (IAGG Global Aging Research Network) http://garn-network.org/index.php have already taken and will take further initiative in this domain. They have pointed out the need to concentrate on aging-in-place to prevent premature nursing home placement. We really need to implement pre-frail and frailty in usual geriatric care worldwide. If we are able to recognize and treat frailty in our clinical practice, it will be a new area for geriatric medicine. At this time, we will be able to develop high level clinical research on biomarkers, imaging and new treatment approaches. Multi-domain or multimodal intervention will be most probably necessary. At the same time, some actions have to be implemented to prevent iatrogenic hospitalization if these frail older adults have to be hospitalized. This move of geriatric medicine in the pre-frail and frail will be cost effective and can give a new rebound for geriatrics, as recommended in a recent European intiatives.

PMID: 22836699 [PubMed - in process]

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Patterns and Costs Associated with Progression of Age-Related Macular Degeneration.

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PURPOSE: To evaluate patterns of disease progression among individuals with age-related macular degeneration (AMD) and to compare costs over time.

DESIGN: Retrospective data analysis using 5% Medicare claims data from 1997 through 2009.

METHODS: Beneficiaries were included if they had no diagnosis of AMD in 1997, were 65 years of age or older, had data through 2009, and had no major ophthalmic conditions. Two cohorts were identified: those who had dry AMD in 1998 (cases) and matched controls who never had AMD.

RESULTS: There were 52 607 beneficiaries who never had AMD and 1184 who were diagnosed with dry AMD in 1998. Among beneficiaries with dry AMD, the disease of 20.4% progressed to the wet form by 2009. From 1999 to 2009, average annual Medicare expenditures increased from $11 265 to $24 494 (cases whose disease did not progress) and from $11 712 to $34 308 (cases whose disease progressed). Among beneficiaries without AMD, expenditures also increased over time (from $4736 in 1999 to $17 473 in 2009), but consistently were lower than cases' expenditures. Considering ophthalmic expenditures, the pattern was more pronounced: beneficiaries without AMD had annual expenditures less than $100, those with dry AMD had expenditures at least 3 times more, and wet AMD beneficiaries' costs were at least 5-fold more than that of those with dry disease. A subgroup analysis of beneficiaries without hypertension revealed similar patterns, although expenditures were lower than in the general population.

CONCLUSIONS: AMD progression seems to be associated with increased annual Medicare expenditures. Findings suggest that halting or slowing disease progression using proven treatment such as Age-Related Eye Disease Study-endorsed vitamins or novel technologies could have a substantial positive impact by lowering public health expenditures.

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Pathogenesis

PLoS One. 2012;7(7):e41309. Epub 2012 Jul 19.

J Clin Invest. 2012 Jul 23. pii: 63816. doi: 10.1172/JCI63816. [Epub ahead of print]

Abnormal vascularization in mouse retina with dysregulated retinal cholesterol homeostasis.

Omarova S, Charvet CD, Reem RE, Mast N, Zheng W, Huang S, Peachey NS, Pikuleva IA.

Abstract

Several lines of evidence suggest a link between age-related macular degeneration and retinal cholesterol maintenance. Cytochrome P450 27A1 (CYP27A1) is a ubiquitously expressed mitochondrial sterol 27-hydroxylase that plays an important role in the metabolism of cholesterol and cholesterol-related compounds. We conducted a comprehensive ophthalmic evaluation of mice lacking CYP27A1. We found that the loss of CYP27A1 led to dysregulation of retinal cholesterol homeostasis, including unexpected upregulation of retinal cholesterol biosynthesis. Cyp27a1-/- mice developed retinal lesions characterized by cholesterol deposition beneath the retinal pigment epithelium. Further, Cyp27a1-null mice showed pathological neovascularization, which likely arose from both the retina and the choroid, that led to the formation of retinal-choroidal anastomosis. Blood flow alterations and blood vessel leakage were noted in the areas of pathology. The Cyp27a1-/- retina was hypoxic and had activated Müller cells. We suggest a mechanism whereby abolished sterol 27-hydroxylase activity leads to vascular changes and identify Cyp27a1-/- mice as a model for one of the variants of type 3 retinal neovascularization occurring in some patients with age-related macular degeneration.

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A2E accumulation influences retinal microglial activation and complement regulation.

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Abstract

Age-related macular degeneration is an outer retinal disease that involves aging and immune dysfunction. In the aging retina, microglia aggregate in the outer retina and acquire intracellular autofluorescent lipofuscin deposits. In this study, we investigated whether accumulation of A2E, a key bisretinoid constituent of ocular lipofuscin, alters the physiology of retinal microglia in pathologically relevant ways. Our findings show that sublethal accumulations of intracellular A2E in cultured retinal microglia increased microglial activation and decreased microglial neuroprotection of photoreceptors. Increased A2E accumulation also lowered microglial expression of chemokine receptors and suppressed microglial chemotaxis, suggesting that lipofuscin accumulation may potentiate subretinal microglial accumulation. Significantly, A2E accumulation altered microglial complement regulation by increasing complement factor B and decreasing complement factor H expression, favoring increased complement activation and deposition in the outer retina. Taken together, our findings highlight the role of microglia in the local control of complement activation in the retina and present the age-related accumulation of ocular lipofuscin in subretinal microglia as a cellular mechanism capable of driving outer retinal immune dysregulation in age-related macular degeneration pathogenesis.

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A novel source of methylglyoxal and glyoxal in retina: implications for age-related macular degeneration.

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Abstract

Aging of retinal pigment epithelial (RPE) cells of the eye is marked by accumulations of bisretinoid fluorophores; two of the compounds within this lipofuscin mixture are A2E and all-trans-retinal dimer. These pigments are implicated in pathological mechanisms involved in some vision-threatening disorders including age-related macular degeneration (AMD). Studies have shown that bisretinoids are photosensitive compounds that undergo photooxidation and photodegradation when irradiated with short wavelength visible light. Utilizing ultra performance liquid chromatography (UPLC) with electrospray ionization mass spectrometry (ESI-MS) we demonstrate that photodegradation of A2E and all-trans-retinal dimer generates the dicarbonyls glyoxal (GO) and methylglyoxal (MG), that are known to modify proteins by advanced glycation endproduct (AGE) formation. By extracellular trapping with aminoguanidine, we established that these oxo-aldehydes are released from irradiated A2E-containing RPE cells. Enzyme-linked immunosorbant assays (ELISA) revealed that the substrate underlying A2E-containing RPE was AGE-modified after irradiation. This AGE deposition was suppressed by prior treatment of the cells with aminoguanidine. AGE-modification causes structural and functional impairment of proteins. In chronic diseases such as diabetes and atherosclerosis, MG and GO modify proteins by non-enzymatic glycation and oxidation reactions. AGE-modified proteins are also components of drusen, the sub-RPE deposits that confer increased risk of AMD onset. These results indicate that photodegraded RPE bisretinoid is likely to be a previously unknown source of MG and GO in the eye.

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Genetics

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Association of Sequence Variation in the CX3CR1 Gene With Geographic Atrophy Age-Related Macular Degeneration in a Greek Population.

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Abstract

Purpose: To explore the association of two single nucleotide polymorphisms (SNPs) in the CX3CR1 gene with grades of age-related macular degeneration (AMD) in a population-based setting. Methods: The Thessaloniki Eye study is a cross-sectional population-based epidemiologic study of chronic eye diseases in Thessaloniki, Greece. A total of 371 subjects were included and classified according to their AMD status. Subjects with AMD Grades 0-1 (n = 188) were compared to those with AMD Grades 2-3 (n = 138), to those with AMD Grade 4 (geographic atrophy) (n = 20) and to those with AMD Grade 5 (neovascular AMD) (n = 25) with regard to the presence of CX3CR1 polymorphisms (V249I and T280M). Polychotomous logistic regression analysis adjusted for age, gender, and smoking was conducted and the log-additive allelic model was preferred. Results: Participants with AMD Grade 4 were approximately three times more likely to carry the VI249 and nine times more likely to carry the II249 alleles, compared to those with AMD Grades 0 -1, whereas those with AMD Grades 2-3 or Grade 5 did not differ. The T280M polymorphism was not associated with either AMD Grades 2-3 or AMD Grades 4 or 5. Conclusion: In this Greek population, after adjusting for known risk factors, increased risk of geographic atrophy (GA) AMD among the carriers of the V249I polymorphism in the CX3CR1 gene was found. Our study failed to reveal any association with the T280M polymorphism reported in previous studies. Additional studies in different ethnic populations using standardized methodology are needed in order to confirm this association.

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Diet

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Improvement of Retinal Function in Early Age-Related Macular Degeneration After Lutein and Zeaxanthin Supplementation: A Randomized, Double-Masked, Placebo-Controlled Trial.

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PURPOSE: To examine the effects of lutein and zeaxanthin supplementation on retinal function using multifocal electroretinograms (mfERG) in patients with early age-related macular degeneration (AMD).

DESIGN: Randomized, double-masked, placebo-controlled trial.

METHODS: One hundred eight subjects with early AMD were randomly assigned to receive 10 mg/d lutein (n = 27), 20 mg/d lutein (n = 27), 10 mg/d lutein plus 10 mg/d zeaxanthin (n = 27), or placebo (n = 27) for 48 weeks. Thirty-six age-matched controls without AMD were also enrolled to compare baseline data with early AMD patients. MfERG responses and macular pigment optical densities (MPODs) were recorded and analyzed at baseline and at 24 and 48 weeks.

RESULTS: There were significant reductions in N1P1 response densities in ring 1 to ring 3 in early AMD patients compared with the controls ($P < .05$), whereas neither N1P1 response densities in ring 4 to ring 6 nor P1 peak latencies significantly changed. After 48-week supplementation, the N1P1 response densities showed significant increases in ring 1 for the 20 mg lutein group and for the lutein and zeaxanthin group, and in ring 2 for the 20 mg lutein group. The increases in MPOD related positively to the increases in N1P1 response density in ring 1 and ring 2 for nearly all active treatment groups. N1P1 response densities in ring 3 to ring 6 or P1 peak latencies in all rings did not change significantly in any group.

CONCLUSION: Early functional abnormalities of the central retina in the early AMD patients could be improved by lutein and zeaxanthin supplementation. These improvements may be potentially attributed to the elevations in MPOD.

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