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Drug treatment

Retina. 2011 Feb 23. [Epub ahead of print]

ONE-YEAR OUTCOMES OF LESS FREQUENT BEVACIZUMAB IN AGE-RELATED MACULAR DEGENERATION.

Sonmez K, Sonmez PA, Ozkan SS, Atmaca LS.

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PURPOSE: To evaluate whether a less frequent bevacizumab dosing schedule after repeated doses in short intervals would be effective in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration.

METHODS: Twenty-seven treatment-naive eyes of patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration participated in this prospective, noncomparative, and interventional study at the Ulucanlar Eye Training and Research Hospital retina clinic. All lesion types were included. Intravitreal injections (1.25 mg/0.05 mL) of bevacizumab were given with a 6-week interval (Day 0, 6 weeks, and 12 weeks) for 3 months and then given every 12-week interval up to 48 weeks. Main outcome measures of treatment were mean change in visual acuity and foveal center point retinal thickness from baseline documented by optical coherence tomography at 6, 12, 24, 36, and 48 weeks. The effects of patient age, baseline visual acuity, lesion composition, and lesion size on final visual acuity and loss of <15 letters of logarithm of the minimum angle of resolution (logMAR) at 48 weeks were also assessed.

RESULTS: Of the 27 eyes, 24 eyes of 24 patients (14 men and 10 women) completed the 48-week follow-up and study protocol. Compared with baseline (0.95 ± 0.27 on Early Treatment Diabetic Retinopathy Study charts), mean best-corrected visual acuity improved to 0.77 ± 0.21 logMAR ($P < 0.001$) at Week 6, to 0.74 ± 0.2 logMAR ($P < 0.001$) at Week 12, to 0.79 ± 0.257 logMAR ($P = 0.03$) at Week 24, to 0.85 ± 0.26 logMAR ($P = 0.54$) at Week 36, and to 0.87 ± 0.27 logMAR ($P = 1$) at Week 48. The baseline mean center point retinal thickness that was 343 ± 64 μm decreased to 236 ± 40 μm ($P < 0.001$) at Week 6, to 222 ± 39 μm ($P < 0.001$) at Week 12, to 237 ± 37 ($P < 0.001$) at Week 24, to 253 ± 44 μm ($P < 0.001$) at Week 36, and to 268 ± 58 μm ($P = 0.002$) at Week 48. The maximal visual benefit obtained during the frequent dosing schedule significantly decreased by doses every 12 weeks at 48 weeks ($P < 0.001$). This decline in the best-corrected visual acuity gain was associated with an increase in the mean center point retinal thickness on optical coherence tomography. Patients aged <70 years and those having a baseline vision of 20/200 or worse were more likely to gain vision at 48 weeks ($P = 0.001$ and $P = 0.02$, respectively). In addition, a lesion ≤4 disk areas at baseline was less likely to lose <15 letters from baseline at 48 weeks ($P = 0.03$). No serious ocular and nonocular adverse events were noted.

CONCLUSION: Although intravitreal bevacizumab administration on a schedule of a 6-week injection interval for 3 months followed by every 12-week interval for neovascular age-related macular degeneration provided an improvement or stabilization in best-corrected visual acuity with anatomical improvement, this dosing strategy is unable to maintain the visual acuity and optical coherence tomography benefits seen with more frequent dosing.

PMID: 21358363 [PubMed - as supplied by publisher]

Retina. 2011 Feb 24. [Epub ahead of print]

INTRAVITREAL RANIBIZUMAB FOR THE TREATMENT OF INFLAMMATORY CHOROIDAL NEOVASCULARIZATION.

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PURPOSE: To evaluate the effect of individualized repeated intravitreal injections of ranibizumab (Lucentis) on visual acuity and central foveal thickness in patients with choroidal neovascular membrane (CNV) associated with various ocular inflammatory clinical entities.

METHODS: Our study was a retrospective, noncomparative, interventional, and observational case series. Sixteen eyes of 15 consecutive patients diagnosed with inflammatory CNV treated with repeated intravitreal injections of ranibizumab were evaluated. The underlying diagnoses were toxoplasmosis (n = 4), serpiginous choroidopathy (n = 2), punctate inner choroidopathy (n = 5), multifocal choroiditis (MFC, n = 3), and scleroderma (n = 2). All patients underwent monthly optical coherence tomography (OCT) scans and fluorescein angiography/indocyanine green angiography every 1 month after every injection and then every 3 months. Optical coherence tomography scans and fluorescein angiography were performed by the same experienced physician. Repeated intravitreal injections were performed when persistent/recurrent fluid on OCT and/or signs of active CNV on angiography were present. Changes in Early Treatment Diabetic Retinopathy Study visual acuity and central foveal thickness were statistically analyzed.

RESULTS: The mean follow-up time was 70.4 ± 24 weeks (17.6 months; range, 44-116 weeks [11-29 months]). The mean number of injections performed was 2.3, and the mean best-corrected visual acuity improved from 55 Early Treatment Diabetic Retinopathy Study letters (logarithm of the minimum angle of resolution, 0.9 ± 0.4 [mean ± SD]) at baseline to 70.3 Early Treatment Diabetic Retinopathy Study letters (logarithm of the minimum angle of resolution, 0.6 ± 0.4) at the end of the follow-up, a statistically significant change compared with baseline ($P < 0.0001$). The mean letter gain was 15.3 letters, and best-corrected visual acuity improved in 14 of 16 patients (88%) and remained stable in 2 patients (12.5%) without any patient demonstrating deterioration. The mean central foveal thickness (although not excessively increased at baseline) improved from 285 ± 20 μm at baseline to 233 ± 21 μm (statistically significant compared with baseline, $P < 0.0001$) at the end of the follow-up. At the end of the follow-up, all patients demonstrated CNV regression, and retinal pigment epithelial atrophy surrounding the regressed CNV was developed in 11 of the 16 eyes (68.8%). During the same period, no CNV recurrence was observed and no injection-related complications such as cataract, retinal detachment, endophthalmitis, or exacerbation of uveitis were noted.

CONCLUSION: Overall, our findings suggest that intravitreal injections of ranibizumab have shown promising results in visual acuity improvement and a decrease in macular thickness in patients with inflammatory CNV. Of course, further studies are needed to confirm the exact benefit and standardize the optimal treatment regimen.

PMID: 21358461 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Feb 25. [Epub ahead of print]

Early Multifocal Electroretinogram Findings during Intravitreal Ranibizumab Treatment for Neovascular Age-related Macular Degeneration.

Campa C, Hagan R, Sahni JN, Brown MC, Beare NA, Heimann H, Harding SP.

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Purpose: To evaluate changes in the multifocal electroretinogram (mfERG) in patients with neovascular age -related macular degeneration (nAMD) undergoing ranibizumab treatment.

Methods: Observational longitudinal prospective study. Treatment-naive patients with nAMD meeting inclusion and exclusion criteria underwent a course of monthly injections of ranibizumab over 3 months. At baseline and month 3 each subject was evaluated with best corrected visual acuity (BCVA), contrast sensitivity (CS), fluorescein and indocyanine green angiography, optical coherence tomography (OCT) and mfERG. Additional mfERG was performed at weeks 1 and 4 and BCVA and OCT at weeks 4 and 8.

Results: Eighteen patients were enrolled. Between baseline and week 12 median BCVA improved from 59 to 69 ETDRS letters (p=0.001), median CS improved from 29 to 30 letters (p=0.05), mean OCT central foveal subfield thickness (CFT) decreased from 294 to 199 µm (p=0.005), mean P1 amplitude density of the mfERG central zone increased from 35.85 to 51.55 nV/°2 (p=0.009). The mfERG response correlated positively with BCVA (F-statistic 22, p-value <0.0001) and negatively with CFT (F-statistic 12.73, p-value 0.00078).

Conclusions: Intravitreal ranibizumab therapy appears to induce an increase of mfERG centrally in patients with nAMD at least in the short term. Longer term studies to investigate the prognostic value of mfERG responses to predict changes in visual acuity in nAMD and other diseases are warranted.

PMID: 21357390 [PubMed - as supplied by publisher]

89Zr-Labeled N-succinyldesferrioxamine-ranibizumab.

Chopra A.

In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2011.

2011 Jan 26 [updated 2011 Feb 24].

Excerpt

The vascular endothelial growth factors (VEGF) are a family of mitogenic glycoproteins (designated VEGF-A thru VEGF-E) that promote angiogenesis by the activation of the VEGF receptors (VEGFR) via a tyrosine kinase (TK) signaling pathway. These growth factors are known to assist in the survival and promotion of malignant tumors by increasing the abnormal neovascularization of the lesions (1). As a result, anti-angiogenic therapy with bevacizumab, a humanized anti-VEGF monoclonal antibody (mAb), its Fab fragment ranibizumab, and small molecule VEGFR TK inhibitors such as sorafenib and sunitinib are often used to treat various types of cancer (2) and other VEGF-related health conditions (3). However, these therapies are not entirely effective due to the development of resistance to the treatments as discussed in detail elsewhere (4). In addition, the efficacy of an anti-angiogenic therapy cannot be reliably assessed with either invasive (e.g., biopsy to measure different histochemical vascular markers) or non-invasive (imaging with [15O]H2O, ultrasound, optical probes, or magnetic resonance) methods (4). Radiolabeled VEGF or anti-VEGFR antibodies have been used to study the VEGF/VEGFR expression profiles of angiogenic tumors with single-photon emission computed tomography or positron emission tomography (PET) imaging in preclinical studies; however, because the expression level of these molecules in the tumor changes with the tumor's development stage, data obtained from these studies often yields inconclusive results (4). PET

imaging with 89Zr-labeled bevacizimab (89Zr-bevacizimab; molecular weight ((mol. wt.) ~150 kDa) was recently shown to be suitable for the determination of VEGF levels in xenograft tumors on athymic nude mice and to predict tumor response to VEGF-dependent anti-angiogenic therapy (5). The physical half-life of 89Zr is ~78.5 h. The main limitation of this imaging agent is its long circulating serum half-life (21 days), and the maximum signal was observed only 4–7 days postinjection (p.i.) of the radiolabeled mAb. In an effort to develop an imaging agent superior to 89Zr-bevacizimab to predict the effectiveness of anti-VEGF therapy, ranibizumab (mol. wt. ~40 kDa) was labeled with 89Zr (89Zr-ranibizumab). For the development, characteristics, and clinical application of ranibizumab, see Ferrara et al. (6). The biodistribution and possible utility of 89Zr-ranibizumab as a tumor-imaging agent to determine the efficacy of sunitinib was investigated in athymic mice bearing SKOV-3 (a human adenocarcinoma cell line), A2780 (a human ovarian cancer cell line), or Colo205 (a human colorectal adenocarcinoma cell line) xenograft tumors (7).

Sections

- Background
- Synthesis
- In Vitro Studies: Testing in Cells and Tissues
- Animal Studies
- Human Studies
- Supplemental Information
- References

PMID: 21370509 [PubMed]Books & Documents

Other treatment & diagnosis

Zhongguo Zhen Jiu. 2011 Jan;31(1):43-5.

[Observation on therapeutic effect of age-related macular degeneration treated with acupuncture].

[Article in Chinese]

Jiao NJ.

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OBJECTIVE: To seek the effective treatment for age-related macular degeneration(AMD).

METHODS: Eighty-four cases (ninety affected eyes) with AMD were randomly devided into an acupuncture group (fifty-six cases, sixty eyes)and a medication group (twenty-eight cases,thirty eyes). In the acupuncture group, Guangming (GB 37), Jingming(BL 1), Cuanzhu (BL 2), Taiyang (EX-HN 5), Sibai (ST 2), Yangbai (GB 14), Tongziliao (GB 1), Fengchi (GB 20), Ganshu (BL 18), Shenshu (BL 23) and Fenglong (ST 40) were punctured. The medication group was treated by oral administration of Vitamin C and Vitamin E and intramuscular injection of Entodon. The therapeutic effects were evaluated after treatment.

RESULTS: The total effective rate was 88.3% (53/60) in acupuncture group which was better than that of 60.0% (18/30) in medication group ($P < 0.05$).

CONCLUSION: Acupuncture has a good clinical effect on AMD.

PMID: 21355157 [PubMed - in process]

Med Hypotheses. 2011 Feb 25. [Epub ahead of print]

Cataract is a self-defence reaction to protect the retina from oxidative damage.

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Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries. Cataract extraction is the most common surgical procedure in developed countries. Lutein (L) and zeaxanthin (Z), retinal carotenoids, are the most powerful retinal anti-oxidants and absorb the harmful blue light. The depletion of L+Z induces the development of the lens opacification-cataract. Cataract reduces the retinal oxidative stress (OS), which causes a reduction of the probability to develop AMD. Oxidative Stress at the retinal level is the common pathway in the development of AMD and cataract. AMD and cataract are not two independent processes. Cataract is a self-defense reaction of the retina to reduce OS and retinal damage. Restoring the anti-oxidative capabilities of the retina by increasing intake of L+Z reduces the likelihood of AMD and cataract. Extracting the opaque lens elevates the retinal OS and increases the rate of AMD.

PMID: 21354712 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Feb 25. [Epub ahead of print]

Spatial Localization of A2E in the Retinal Pigment Epithelium.

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Purpose: Lipofuscin, a fluorescent lysosomal pigment made up of lipophilic molecules, is associated with age related pathophysiological processes in the retinal pigment epithelium (RPE). The best characterized components of lipofuscin are A2E and its oxides but a direct spatial correlation with lipofuscin has not previously been possible.

Methods: We mapped lipofuscin fluorescence across the RPE of Abca4(-/-) and Sv129 (background strain control) mice. In the same tissues, we determined the spatial distribution of A2E and its oxides by utilizing the high molecular specificity of matrix-assisted laser desorption-ionization imaging mass spectrometry (MALDI-IMS). The fluorescence and tandem mass spectra taken directly from the tissue were compared to those of synthetic A2E standard.

Results: In 2 month old mice, A2E was found in the center of the RPE tissue and with age A2E increased across the tissue. At high levels of A2E there was a marked correlation between A2E and lipofuscin, but at low levels this correlation diminished. The distributions of the oxidized forms of A2E were also determined. The amount of oxidation on A2E remained constant over 6 months, implying that A2E is not becoming increasingly oxidized with age in this time frame.

Conclusions: This report is the first description of the spatial imaging of a specific retinoid from fresh tissue and the first description of a direct correlation of A2E with lipofuscin. The molecule-specific imaging of lipofuscin components from the RPE suggests wide applicability to other small molecules and pharmaceuticals for the molecular characterization and treatment of age-related macular degeneration.

PMID: 21357388 [PubMed - as supplied by publisher]

The Impact of Vision Impairment on Vision-Specific Quality of Life in Germany.

Invest Ophthalmol Vis Sci. 2011 Feb 25. [Epub ahead of print]

Finger RP, Fenwick E, Marella M, Dirani M, Holz FG, Chiang PP, Lamoureux EL.

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Background: To validate the German--translated Impact of Vision Impairment (IVI) questionnaire, a vision-specific quality of life (QoL) scale, and determine the relationship between the severity of vision impairment, ocular conditions and vision-related QoL.

Methods: This was a clinical-based, cross-sectional study with 184 patients with low vision recruited from an outpatient clinic at a German eye hospital. Participants underwent a clinical examination and completed the German IVI scale. The validity of the IVI scale was assessed using Rasch analysis. The main outcome measure was the overall functional and emotional score provided by the IVI.

Results: Overall, there were more female (n=111, 60.3%) than male participants. Participants' mean±SD [standard deviation] age and visual acuity in the better eye was 69.0±15.5 years and. 0.41±0.35 LogMAR, respectively. The main cause of vision loss was age-related macular degeneration (n=54, 29.3%). Rasch analysis demonstrated the validity of the German IVI to assess VRQoL through two subscales: vision-specific functioning and emotional well-being. In adjusted multivariate analysis models those with mild, or moderate/severe vision impairment reported significantly poorer vision-specific functioning (mean change -6.5, p=0.018 and -11.98, p<0.001 for mild and moderate/severe VI, respectively) and emotional well-being (mean change -2.35, p=0.043 and -3.13, p=0.004 for mild and moderate/severe VI respectively) compared to non visually impaired patients.

Conclusions: Using a psychometrically valid German IVI, even mild vision impairment was independently associated with poor VRQoL. These findings reinforce the importance of early preventative and rehabilitative efforts to prevent longitudinal deterioration in vision loss.

PMID: 21357395 [PubMed - as supplied by publisher]

Retina. 2011 Feb 24. [Epub ahead of print]

DISPLAYED REFLECTIVITY OF CHOROIDAL NEOVASCULAR MEMBRANES BY OPTICAL COHERENCE TOMOGRAPHY CORRELATES WITH PRESENCE OF LEAKAGE BY FLUORESCEIN ANGIOGRAPHY.

Giani A, Esmaili DD, Luiselli C, Cigada M, Salvetti P, Miller JW, Staurenghi G.

From the *Retina Service, Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts; and †Eye Clinic, Department of Clinical Science "Luigi Sacco", Sacco Hospital, University of Milan, Milan, Italy.

PURPOSE: To evaluate and correlate the displayed optical reflectivity of choroidal neovascularization (CNV) subretinal material on spectral-domain optical coherence tomography with the presence of dye leakage on fluorescein angiography (FA).

METHODS: Thirty-nine eyes of 39 patients with a diagnosis of predominantly classic CNV from age-related macular degeneration underwent simultaneous spectral-domain optical coherence tomography and FA imaging. Eight patients had a newly diagnosed untreated CNV. Thirty-one patients had already been treated with anti-vascular endothelial growth factor agents. In 18 of these eyes, CNV lesions showed persistent leakage by FA. In 13 eyes, CNV lesions did not show leakage by FA. Subretinal CNV material boundaries visualized on spectral-domain optical coherence tomography B-scans were manually traced, and optical reflectivity was calculated using the mean grayscale value. To account for variable image brightness, the retinal pigment epithelial reflectivity was measured. The absolute difference between CNV material and retinal pigment epithelial reflectivity (ΔREF) from the three groups (newly diagnosed CNV, previously treated CNV showing FA leakage, and previously treated CNV not showing FA leakage) was compared.

RESULTS: In untreated lesions, ΔREF was significantly higher compared with previously treated, but still leaky, CNV (P < 0.0001). Lesions showing FA leakage had significantly higher ΔREF compared with those that did not display leakage (P < 0.0001).

CONCLUSION: The displayed reflectivity of subretinal CNV material in spectral-domain optical coherence tomography appears to be an important parameter that can provide information regarding the FA leakage status.

PMID: 21358457 [PubMed - as supplied by publisher]

PLoS One. 2011 Feb 15;6(2):e17106.

CCR3 and Choroidal Neovascularization.

Li Y, Huang D, Xia X, Wang Z, Luo L, Wen R.

Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, United States of Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly in industrialized countries. The "wet" AMD, characterized by the development of choroidal neovacularization (CNV), could result in rapid and severe loss of central vision. The critical role of vascular endothelial growth factor A (VEGF-A) in CNV development has been established and VEGF-A neutralization has become the standard care for wet AMD. Recently, CCR3 was reported to play an important role in CNV development and that CCR3 targeting was reported to be superior to VEGF-A targeting in CNV suppression. We investigated the role of CCR3 in CNV development using the Matrigel induced CNV and found that in both rats and mice, CNV was well-developed in the control eyes as well as in eyes treated with CCR3 antagonist SB328437 or CCR3 neutralizing antibodies. No statistically significant difference in CNV areas was found between the control and SB328437 or CCR3-ab treated eyes. Immunostaining showed no specific expression of CCR3 in or near CNV. In contrast, both VEGF-A neutralizing antibodies and rapamycin significantly suppressed CNV. These results indicate that CCR3 plays no significant role in CNV development and question the therapeutic approach of CCR3 targeting to suppress CNV. On the other hand, our data support the therapeutic strategies of VEGF-A and mTOR (mammalian target of rapamycin) targeting for CNV.

PMID: 21358803 [PubMed - in process]PMCID: PMC3039674

Eur J Ophthalmol. 2011 Feb 25. pii: E3C79688-4CFC-4A5C-9FCE-1874D81EF975. [Epub ahead of print]

Phacoemulsification in eyes with neovascular AMD treated with anti-VEGF injections.

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Purpose. To evaluate visual results of phacoemulsification in eyes with neovascular age-related macular degeneration (AMD) treated with anti-vascular endothelial growth factor (VEGF) intravitreal injections.

Methods. This retrospective noncomparative interventional case-series study assessed best-corrected visual acuity (BCVA) at 4 timepoints: 1) baseline, immediately before first anti-VEGF injection; 2) preoperative, immediately before phacoemulsification; 3) postoperative, 1 month after phacoemulsification; 4) endpoint, at the last visit. Anti-VEGF retreatment regimen was based only on optical coherence tomography. The median time between anti-VEGF injections was evaluated for the time period before and after phacoemulsification.

Results. Sixteen eyes of 16 patients were included. The median (range) baseline, preoperative, postoperative, and endpoint BCVA was 0.7 (0.3-1.3), 0.72 (0.4-1.3), 0.5 (0.05-1.0), and 0.36 (0.0-1.0) logMAR, respectively. Best-corrected visual acuity significantly improved after phacoemulsification (mean 3 logMAR lines) and remained stable during follow-up (median 14 months, range 7-28). There was no

statistically significant difference in the median time interval between injections before phacoemulsification and after phacoemulsification.

Conclusions. Phacoemulsification significantly improved BCVA in patients with choroidal neovascular AMD. This effect persisted during follow-up with no increased need for anti-VEGF injections to keep macula dry.

PMID: 21360482 [PubMed - as supplied by publisher]

MAbs. 2010 Mar;2(2):176-80.

Therapeutic antibodies in ophthalmology: Old is new again.

Magdelaine-Beuzelin C, Pinault C, Paintaud G, Watier H.

Abstract

More than a century after the first successful use of serotherapy, antibody-based therapy has been renewed by the availability of recombinant monoclonal antibodies. As in the past, current clinical experience has prompted new pharmacological questions and induced much debate among practitioners, notably in the field of ophthalmology. An examination of the history of antibodies as treatments for ocular disorders reveals interesting parallels to the modern era. The fact that a treatment administered by a systemic route could be efficacious in a local disease was not widely accepted and the "chemical" nature of antibodies was not clearly understood in the late 19th century. Clinical studies by Henry Coppez, a Belgian ophthalmologist, established in 1894 that antidiphtheric antitoxins could be used to treat conjunctival diphtheria. Nearly 20 years later, Coppez and Danis described age-related macular degeneration, a disorder which today benefits from ranibizumab therapy. The product, a locally-administered recombinant monoclonal Fab fragment, is directed against vascular endothelial growth factor A. Interestingly, its full-size counterpart, bevacizumab, which is approved for the treatment of solid tumors, has also demonstrated efficacy in age-related macular degeneration when administered either intravenously or locally, which raises new questions about antibody pharmacology and biodistribution.In order to shed some light on this debate, we recount the early history of serotherapy applied to ophthalmology, review the exact molecular differences between ranibizumab and bevacizumab, and discuss what is known about IgG and the blood-retina barrier and the possible role of FcRn, an IgG transporter.

PMID: 21358858 [PubMed - in process]PMCID: PMC2840236

Chin Med J (Engl). 2011 Feb;124(4):541-5.

Long-term effect of prophylactic laser treatment for bilateral soft drusen.

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BACKGROUND: Large drusen is a known risk factor for the development of late complications of age-related macular degeneration (AMD) and drusen reduction has been found by our previous study. To prospectively evaluate the efficacy and safety of prophylactic laser treatment in Chinese patients with bilateral soft drusen, we examined the structure and function of the macula 8 years after treatment.

METHODS: Ten patients with more than 10 soft drusen (> 125 mm) and best corrected visual acuity ≥ 20/25 in each eye participated in the study. One eye, with relatively more drusen, was exposed to an argon laser (514 nm) to achieve a barely visible retinal lesion. The contralateral eye was used as a control. Fluorescein angiography, Amsler tests, Fourier-domain optical coherence tomography and visual evoked potential tests were carried out 8 years later.

RESULTS: No choroidal neovascularization was seen in the laser-treated eyes or control eyes. There were no significant differences in visual acuity or P100 latency and amplitude between the laser treated eyes and contralateral eyes (t = 1.685, 1.184; P > 0.05). The thickness of the retinal pigment epithelium of the treated eyes was less than that of the contralateral eyes (t = -4.540; P < 0.05). The full retinal thickness in treated eyes was slightly, but insignificantly, reduced relative to contralateral eyes (t = -1.746; P > 0.05).

CONCLUSIONS: The treatment was associated with a reduction in retinal pigment epithelium thickness elevation compared with the contralateral eyes. Macular function was not impaired.

PMID: 21362278 [PubMed - in process]

Chin Med J (Engl). 2011 Jan;124(2):253-7.

Characteristics of fundus autofluorescence in cystoid macular edema.

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BACKGROUND: Fundus autofluorescence (FAF) imaging is a fast and noninvasive technique developed over the last decade. The authors utilized fluorescent properties of lipofuscin to study the health and viability of the retinal pigment epithelium (RPE)-photoreceptor complex. Observing the intensity and distribution of FAF of various retinal diseases is helpful for ascertaining diagnosis and evaluating prognosis. In this study, we described the FAF characteristics of cystoid macular edema (CME).

METHODS: Sixty-two patients (70 eyes) with CME were subjected to FAF and fundus fluorescein angiography (FFA) by a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph 2 (HRA2)). Characteristics of FAF images were compared with FFA images.

RESULTS: FAF intensity in normal subjects was highest at the posterior pole and dipped at the fovea. All cases of CME showed fluorescein dye accumulated into honeycomb-like spaces in macular and formated a typical petaloid pattern or atypical petaloid pattern in the late phases of the angiography. Sixty-one eyes with CME on FAF images showed mild or moderate hyperautofluorescence petaloid pattern in fovea, the FAF patterns of these CME was perfectly corresponding with shape in their FFA images; nine eyes with CME secondary to exudative age related macular degeneration (AMD) showed expansion of the hypoautofluorescence without petaloid pattern in macula.

CONCLUSION: FAF imaging can be used as a new rapid, non-invasive and ancillary technique in the diagnosis of the majority of CME, except for AMD and small part of other fundus diseases.

PMID: 21362376 [PubMed - in process]

Mol Vis. 2011 Feb 23;17:576-82.

Coll Antropol. 2010 Apr;34 Suppl 2:21-3.

Progression of age related maculopathy in phakic versus pseudophakic eyes.

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Abstract

Age-related maculopathy (ARM) is one of the leading causes of central visual acuity loss in older western population. Many factors are responsible for the fast development of ARM. One of this is significant

increases of optical radiations through artificial lens after removal of the catarctous lens. The aim of this study was to compare progression of ARM in phakic and pseudophakic patients and to calculate the possibility ofpseudophakia as a risk factor for faster progression of ARM. Medical records of 76 patients, older than 60 years (32 male and 44 female) with early forms of ARM were randomly evaluated. They had undergone cataract removal by phacoemulsification with intraocular lens implantation from January 2002 to December 2006 at the Department of Ophthalmology, Rijeka University Hospital, Croatia. Patients were examined two weeks after the surgery and followed up for two years. The control group consisted of 48 patients (21 males and 27 females) with also early forms of ARM, older than 60 years, examined at the Policlinic Department from January 2006 to December 2006 and followed up at least for two years without any cataract surgery. Comparing progression of ARM in these two groups, a total of 19 patients (25%) in pseudophakic group showed progression to late forms of ARM, but only 6 patients (12.5 %) in the control group developed these aggressive ARM forms. More aggressive forms of ARM in pseudophakic group indicate that pseudophakia should be considered as a risk factor for development of ARM.

PMID: 21302700 [PubMed - indexed for MEDLINE]

Angiogenin in age-related macular degeneration.

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PURPOSE: Age-related macular degeneration (AMD) is a common blinding disease in the elderly population. AMD is frequently complicated by choroidal neovascularization, causing irreversible losses in visual acuity. Proteins that induce pathologic angiogenesis in other systems include angiogenin, a small protein involved in angiogenesis in tumor metastases. Our goal was to determine if angiogenin participates in angiogenesis during choroidal neovascular membrane formation in AMD.

METHODS: The expression of angiogenin in the human retina and retinal pigment epithelium (RPE)-choroid was determined using reverse-transcription (RT)-PCR and immunoblotting. Localization of angiogenin in human control eyes and in eyes with choroidal neovascularization was determined using immunohistochemistry. Potential angiogenin-mediated effects on endothelial cell migration, as well as angiogenin internalization by Rf/6a cells, were determined.

RESULTS: Angiogenin was synthesized by the human choroid and retina and localized to normal and pathologic vasculature. Angiogenin did not change the migratory behavior of Rf/6a chorioretinal endothelial cells; however, these cells did internalize exogenous angiogenin in culture.

CONCLUSIONS: Chorioretinal endothelial cells bind and internalize angiogenin, a protein localized to the choroid in normal eyes, as well as in some drusen and in neovascular membranes in AMD eyes. Angiogenin has been shown to participate in angiogenesis in other tissues. Although angiogenin does not increase the migratory behavior of these cells, it may play a role in other aspects of endothelial cell activation in neovascular AMD.

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Vascular endothelial growth factor-B gene transfer exacerbates retinal and choroidal neovascularization and vasopermeability without promoting inflammation.

Zhong X, Huang H, Shen J, Zacchigna S, Zentilin L, Giacca M, Vinores SA.

PURPOSE: The role of vascular endothelial growth factor (VEGF)-B in the eye is poorly understood. The present study was conducted to evaluate the effect of overexpression of VEGF-B via adeno-associated

virus (AAV) gene transfer on ocular angiogenesis, inflammation, and the blood-retinal barrier (BRB).

METHODS: Three recombinant AAV vectors were prepared, expressing the 167 (AAV-VEGF-B167) or 186 amino acid isoform (AAV-VEGF-B186) of VEGF-B or the green fluorescent protein (GFP) reporter gene (AAV-GFP). Approximately 1×10(9) viral genome copies of AAV-VEGF-B167, AAV-VEGF-B186, or AAV-GFP were intraocularly injected. The efficacy of the gene transfer was assessed by directly observing GFP, by immunohistochemistry, or by real-time PCR. A leukostasis assay using fluorescein isothiocyanate-conjugated Concanavalin A was used to evaluate inflammation. The BRB was assessed using a quantitative assay with (3)H-mannitol as a tracer. Retinal neovascularization (NV) was assessed at postnatal day 17 in oxygen-induced ischemic retinopathy after intravitreal injection of AAV-VEGF-B in left eyes and AAV-GFP in right eyes at postnatal day 7. Two weeks after injection of AAV vectors, choroidal NV was generated by laser photocoagulation and assessed 2 weeks later.

RESULTS: GFP expression was clearly demonstrated, primarily in the retinal pigment epithelium (RPE) and outer retina, 1-6 weeks after delivery. mRNA expression levels of VEGF-B167 and VEGF-B186 were 5.8 and 12 fold higher in the AAV-VEGF-B167- and AAV-VEGF-B186-treated groups, respectively. There was no evidence of an inflammatory response or vessel abnormality following injection of the vectors in normal mice; however, VEGF-B increased retinal and choroidal neovascularization. AAV-VEGF-B186, but not AAV-VEGF-B167, enhanced retinal vascular permeability.

CONCLUSIONS: VEGF-B overexpression promoted pathological retinal and choroidal NV and BRB breakdown without causing inflammation, which is associated with the progression of diabetic retinopathy and age-related macular degeneration, showing that these complications are not dependent on inflammation. VEGF-B targeting could benefit antiangiogenic therapy.

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Polyurethanes as supports for human retinal pigment epithelium cell growth.

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Purpose: The transplant of retinal pigment epithelium (RPE) cells on supports may well be an effective therapeutic approach to improve the visual results of patients with age-related macular degeneration. In this study, two biodegradable polyurethanes were investigated as supports for human RPE cells (ARPE-19).

Methods: Polyurethane aqueous dispersions based on poly(caprolactone) and/or poly(ethylene glycol) as soft segments, and isophorone diisocyanate and hydrazine as hard segments were prepared. Polyurethane films were produced by casting the dispersions and allowing them to dry at room temperature for one week. The ARPE-19 cells were seeded onto the polyurethane films and they were investigated as supports for in vitro adhesion, proliferation, and uniform distribution of differentiated ARPE-19 cells. Additionally, the in vivo ocular biocompatibility of the polyurethane films was evaluated.

Results: The RPE adhered to and proliferated onto the polyurethane supports, thus establishing cell-PUD surface interactions. Upon confluence, the cells formed an organized monolayer, exhibited a polygonal appearance, and displayed actin filaments which ran along the upper cytoplasm. At 15 days of seeding, the occluding expression was confirmed between adjacent cells, representing the barrier functionality of epithelial cells on polymeric surfaces and the establishment of cell-cell interactions. Results from the in vivo study indicated that polyurethanes exhibited a high degree of short-term intraocular biocompatibility.

Conclusions: Biodegradable polyurethane films display the proper mechanical properties for an easy transscleral-driven subretinal implantation and can be considered as biocompatible supports for a functional ARPE-19 monolayer.

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Is quantitative spectral-domain superior to time-domain optical coherence tomography (OCT) in eyes with age-related macular degeneration?

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Purpose: The aim of this study was to determine the variability of macular map measurements, for two generations of optical coherence tomography (OCT) instruments, in eyes with wet age related macular degeneration (AMD) and low visual acuity.

Methods: Patients were examined with Stratus OCT and Cirrus HD-OCT. The macular thickness was assessed with the 'macular thickness map scan' and 'fast protocol' in Stratus and with the 512 × 128 and 200 × 200 cube protocols in Cirrus OCT. Two measurements were taken one directly after the other, at the first visit to analyse repeatability. Approximately 1 week later, a third measurement was taken to analyse reproducibility. In Cirrus OCT, a manual correction of foveal location was also performed. Repeatability and reproducibility were calculated as a coefficient of variance (CoV) and a coefficient of repeatability/reproducibility.

Results: Repeatability for central macular thickness (expressed as CoV) was about three per cent for all protocols, and the coefficient of repeatability between 34 and 54 μm. Reproducibility (also expressed as CoV) was between four to seven per cent and coefficient of repeatability between 64 and 89 μm. After manual adjustment of foveal location in Cirrus OCT, the coefficient of repeatability improved to 12-18 μm, and the coefficient of reproducibility to 44-47 μm.

Conclusions: In eyes affected by wet AMD, there were small differences in repeatability and reproducibility when comparing quantitative maps in Stratus and Cirrus OCT. However, when the software for manual correction of foveal position in Cirrus OCT was used, the variability decreased markedly, and the repeatability was close to what had been reported in normal eyes, demonstrating a significant, potential advantage of spectral-domain over time-domain OCT.

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Epidemiology & pathogenesis

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Regulation of VEGF expression in human retinal cells by cytokines: implications for the role of inflammation in age-related macular degeneration.

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Abstract

Chronic inflammation is implicated in the pathogenesis of age-related macular degeneration (AMD). Choroidal neovascularization (CNV) observed in exudative form of AMD results in vision loss. Human retinal pigment epithelial cell (HRPE) layer and choroidal tissue are the primary pathological sites in AMD. Pathological and therapeutic evidences have strongly indicated the VEGF molecules (VEGFs) as critical components in CNV pathogenesis. In these studies, we used human primary HRPE and choroidal fibroblast cells (HCHF) prepared from adult donor eyes. The effects of inflammatory cytokine (IFN-γ + TNF-α + IL-1β) mix (ICM) on global gene expression profiles in HRPE cells, revealed 10 and 9 fold increase in VEGF-A and VEGF-C expression respectively. The microarray results were validated by quantitative RT-PCR and

secretion of VEGFs proteins. IL-1β is the most potent in inducing VEGFs secretion followed by IFN-γ and TNF-α, and the secretion was more effective in the presence of two and three cytokines. NFκB and JAK-STAT pathway, but not HIF-1α, Sp-1, Sp-3 and STAT-3, transcription factors were up regulated and translocated to nucleus by ICM treatment. The mRNA levels of VEGF-A and VEGF-C and secretion of these proteins were also significantly enhanced by ICM in HCHF cells. The secretion of other angiogenic molecules, PEDF, SDF-1α, endostatin and angiopoietins was not affected by ICM. Our results show that the inflammatory cytokines enhance secretion of VEGF-A and VEGF-C by HRPE and HCHF cells. These studies indicate that VEGFs secreted by these cells initiate and promote pathological choroidal and retinal noevascularization processes in AMD. J. Cell. Physiol. © 2011 Wiley Periodicals, Inc.

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Genetics

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The choice of null distributions for detecting gene-gene interactions in genome-wide association studies.

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BACKGROUND : In genome-wide association studies (GWAS), the number of single-nucleotide polymorphisms (SNPs) typically ranges between 500,000 and 1,000,000. Accordingly, detecting gene-gene interactions in GWAS is computationally challenging because it involves hundreds of billions of SNP pairs. Stage-wise strategies are often used to overcome the computational difficulty. In the first stage, fast screening methods (e.g. Tuning ReliefF) are applied to reduce the whole SNP set to a small subset. In the second stage, sophisticated modeling methods (e.g., multifactor-dimensionality reduction (MDR)) are applied to the subset of SNPs to identify interesting interaction models and the corresponding interaction patterns. In the third stage, the significance of the identified interaction patterns is evaluated by hypothesis testing.

RESULTS : In this paper, we show that this stage-wise strategy could be problematic in controlling the false positive rate if the null distribution is not appropriately chosen. This is because screening and modeling may change the null distribution used in hypothesis testing. In our simulation study, we use some popular screening methods and the popular modeling method MDR as examples to show the effect of the inappropriate choice of null distributions. To choose appropriate null distributions, we suggest to use the permutation test or testing on the independent data set. We demonstrate their performance using synthetic data and a real genome wide data set from an Aged-related Macular Degeneration (AMD) study.

CONCLUSIONS : The permutation test or testing on the independent data set can help choosing appropriate null distributions in hypothesis testing, which provides more reliable results in practice.

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Systemic low-molecular weight drug delivery to pre-selected neuronal regions.

Campbell M, Humphries MM, Kiang AS, Nguyen AT, Gobbo OL, Tam LC, Suzuki M, Hanrahan F, Ozaki E, Farrar GJ, Kenna PF, Humphries P.

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Abstract

We describe a procedure for controlled, periodic, reversible modulation of selected regions of the blood-brain barrier (BBB) or the inner-blood-retina barrier (iBRB) based on incorporation into an AAV-2/9 vector of a doxycycline-inducible gene encoding shRNA targeting claudin-5, one of 30 or so proteins constituting the BBB and iBRB. The vector may be introduced stereotaxically into pre-selected regions of the brain or into the retina, rendering these regions permeable to low-molecular weight compounds up to approximately 1 kDa for the period of time during which the inducing agent, doxycycline, is administered in drinking water, but excluding potentially toxic higher molecular weight materials. We report on the use of barrier modulation in tandem with systemic drug therapy to prevent retinal degeneration and to suppress laser-induced choroidal neovascularization (CNV), the latter being the hallmark pathology associated with the exudative, or wet, form of age-related macular degeneration (AMD). These observations constitute the basis of a minimally invasive systemic therapeutic modality for retinal diseases, including retinitis pigmentosa and AMD, where, in early stage disease, the iBRB is intact and impervious to systemically administered drugs. →See accompanying Closeup by Rossi DOI 10.1002/emmm.201100132.

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Pre-clinical

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Nanoceria inhibit the development and promote the regression of pathologic retinal neovascularization in the vldlr knockout mouse.

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Abstract

Many neurodegenerative diseases are known to occur and progress because of oxidative stress, the presence of reactive oxygen species (ROS) in excess of the cellular defensive capabilities. Age related macular degeneration (AMD), diabetic retinopathy (DR) and inherited retinal degeneration share oxidative stress as a common node upstream of the blinding effects of these diseases. Knockout of the Vldlr gene results in a mouse that develops intraretinal and subretinal neovascular lesions within the first month of age and is an excellent model for a form of AMD called retinal angiomatous proliferation (RAP). Cerium oxide nanoparticles (nanoceria) catalytically scavenge ROS by mimicking the activities of superoxide dismutase and catalase. A single intravitreal injection of nanoceria into the Vldlr-/- eye was shown to inhibit: the rise in ROS in the Vldlr-/- retina, increases in vascular endothelial growth factor (VEGF) in the photoreceptor layer, and the formation of intraretinal and subretinal neovascular lesions. Of more therapeutic interest, injection of nanoceria into older mice (postnatal day 28) resulted in the regression of existing vascular lesions indicating that the pathologic neovessels require the continual production of excessive ROS. Our data demonstrate the unique ability of nanoceria to prevent downstream effects of oxidative stress in vivo and support their therapeutic potential for treatment of neurodegenerative diseases such as AMD and DR.

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Expression of Complement Component 3 (C3) from an Adenovirus leads to Pathology in the Murine Retina.

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Purpose: Activation of complement has been implicated as one of the major causes of age-related macular degeneration (AMD). Evidence is accumulating for a role of complement in other retinal diseases, such as diabetic retinopathy and proliferative vitreoretinopathy. Due to the paucity of animal models which directly investigate the role of complement in retinal pathology, we sought to develop a model of increased complement expression and activation, specifically in murine retina.

Methods: We constructed a recombinant adenovirus expressing murine complement component 3 (C3, AdcmvC3). Adult mice were injected in the subretinal space with either AdcmvC3 or a control virus, AdcmvGFP. After one to two weeks of exogenous C3 expression, mice were analyzed by scotopic electroretinogram and fluorescein angiography. Eyes were harvested for histological, immunohistochemical, and quantitative RT-PCR analyses.

Results: Mice injected with C3-expressing adenovirus exhibited significantly increased vascular permeability, endothelial cell proliferation and migration, RPE atrophy, loss of photoreceptor outer segments, reactive gliosis, retinal detachment, and reduced retinal function relative to those injected with a control adenovirus. Deposition of the membrane attack complex was observed on endothelial cells and photoreceptor outer segments.

Conclusions: Adenovirus mediated delivery of C3 to murine RPE induces significant functional and anatomical changes which reproduce many of the features of AMD, as well as those of other retinal diseases. This novel model may be useful in assessing the role of complement in retinal pathology, as well as in developing anti-complement therapies for retinal diseases associated with complement activation.

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