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MD Research News

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Drug Treatment

Clin Exp Optom. 2011 Mar 9. doi: 10.1111/j.1444-0938.2011.00589.x. [Epub ahead of print]

Ranibizumab in the treatment of choroidal neovascularisation due to age-related macular degeneration: an optical coherence tomography and multifocal electroretinography study.

Moschos MM, Brouzas D, Chatziralli IP, Ladas I.

Department of Ophthalmology, University of Athens, Athens, Greece E-mail: moschosmarilita@yahoo.fr.

Background: The aim of this study was to evaluate, by optical coherence tomography (OCT) and multifocal electroretinography (mfERG), the macular function of eyes with choroidal neovascularisation due to age-related macular degeneration (AMD) before and after the intravitreal use of ranibizumab.

Methods: Fifteen eyes with choroidal neovascularisation due to AMD were studied with OCT and mfERG before, during and at the end of the treatment, one year after the first injection of ranibizumab. The eyes received 0.5 mg ranibizumab every month for the first three months, followed by doses every three months. Thus, during the 12-month study, a total of six ranibizumab injections were given.

Results: The level of visual acuity increased significantly with time. A linear mixed-effect analysis showed a borderline negative association between the amount of foveal thickness and time, with a decrease in the mean foveal thickness for one time increment. The retinal response density of the mfERG showed a significant increase in ring 1 and remained almost unchanged in ring 2, whereas there was a statistically insignificant increase in ring 3. Finally, the mean latency remained unchanged throughout the 12 months of treatment in all three rings.

Conclusion: The intravitreal use of ranibizumab might result in an increase of the mfERG in the foveal area. Only a borderline inverse association was shown between the amount of foveal thickness and time. Also, the level of visual acuity statistically significantly improved over time. Randomised long-term clinical trials are needed to determine the potential clinical benefit of ranibizumab.

PMID: 21385210 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2011;5:167-70. Epub 2011 Feb 11.

Foveal atrophy and macular hole formation following intravitreal ranibizumab with/without photodynamic therapy for choroidal neovascularization secondary to age-related macular degeneration.

Rishi P, Kasinathan N, Sahu C.

Shri Bhagwan Mahavir Vitreoretinal Services, Sankara Nethralaya, 18 College Road, Chennai-600006. Tamil Nadu, India.

BACKGROUND: To report the occurrence of foveal atrophy and macular hole formation following intravitreal ranibizumab with or without photodynamic therapy for choroidal neovascularization caused by age-related macular degeneration.

METHODS: This was a retrospective, interventional case series, in which 78 eyes of 76 patients were treated for wet age-related macular degeneration between February 2007 and August 2007. Of these, three eyes developed foveal atrophy following treatment. Two eyes underwent combination photodynamic therapy and intravitreal ranibizumab, and one eye underwent intravitreal ranibizumab alone. One of the two eyes that underwent combination therapy progressed to develop a macular hole.

RESULTS: On the first follow-up visit, all three eyes showed thinning of the fovea on optical coherence tomography. Subsequently, treatment was continued with repeat intravitreal ranibizumab injections. At the last follow-up, although choroidal neovascularization regressed in all eyes, extensive foveal atrophy developed in two eyes with macular hole formation in one eye.

CONCLUSION: The possibility of foveal atrophy and macular hole formation must be borne in mind before initiating ranibizumab in combination with or without photodynamic therapy. However, larger studies with longer follow-up are required to understand such adverse effects better.

PMID: 21383944 [PubMed - in process]PMCID: PMC3045065

Clin Ophthalmol. 2011;5:161-5. Epub 2011 Feb 8.

Intravitreal ranibizumab for symptomatic drusenoid pigment epithelial detachment without choroidal neovascularization in age-related macular degeneration.

Gallego-Pinazo R, Marina A, Suelves-Cogollos, Francés-Muñoz E, Millán JM, Arevalo JF, Mullor JL, Díaz-Llopis M.

Department of Ophthalmology, Hospital Universitario La Fe, Valencia, Spain;

BACKGROUND: The aim of our study was to evaluate the functional and anatomic outcomes of intravitreal ranibizumab for the treatment of symptomatic drusenoid pigment epithelial detachment without choroidal neovascularization in age-related macular degeneration.

METHODS: This was a prospective, single-center, uncontrolled, interventional pilot study. Six consecutive eyes (six patients) with drusenoid pigment epithelial detachment with a visual acuity of 20/63 to 20/100 and no evidence of choroidal neovascularization in age-related macular degeneration participated. Patients were given at least one intravitreal ranibizumab injection and were followed for a mean of 66.67 ± 10.3 weeks. Main outcome measures included best-corrected visual acuity (BCVA) measured by Early Treatment Diabetic Retinopathy Study charts and optical coherence tomography, and central macular thickness measured by optical coherence tomography.

RESULTS: The mean number of intravitreal ranibizumab injections was 3.0 at the end of follow-up. Regarding BCVA and optical coherence tomography, 33.3% of eyes gained between 19 and 21 letters of BCVA, with a median decrease in central macular thickness of 21 μm. There was a statistically significant difference between baseline and final BCVA (P = 0.046). There was a positive correlation between intraretinal fluid by optical coherence tomography and improved BCVA after intravitreal ranibizumab. Metamorphopsia disappeared completely after the first injection in all subjects, with no further recurrences. No patient developed choroidal neovascularization or atrophic changes.

CONCLUSION: Intravitreal ranibizumab demonstrated anatomic and functional benefit in patients with symptomatic drusenoid pigment epithelial detachment without choroidal neovascularization in age-related macular degeneration. Further long-term, randomized, controlled trials should be performed to confirm our

preliminary results.

PMID: 21383943 [PubMed - in process]PMCID: PMC3045064

Retina. 2011 Mar 9. [Epub ahead of print]

COMBINATION TREATMENT WITH INTRAVITREAL INJECTION OF RANIBIZUMAB AND REDUCED FLUENCE PHOTODYNAMIC THERAPY FOR CHOROIDAL NEOVASCULARIZATION SECONDARY TO ANGIOID STREAKS: Preliminary Clinical Results of 12-Month Follow-Up.

Artunay O, Yuzbasioglu E, Rasier R, Sengul A, Senel A, Bahcecioglu H.

From the Department of Ophthalmology, Istanbul Bilim University, Istanbul, Turkey.

BACKGROUND: To evaluate combination treatment with intravitreal ranibizumab injection and reduced fluence photodynamic therapy for choroidal neovascularization associated with angioid streaks.

METHODS: This is an interventional case series of 10 previously untreated eyes of 10 patients with choroidal neovascularization secondary to angioid streaks. All eyes were treated with reduced fluence photodynamic therapy using 25 J/cm, immediately followed by intravitreal ranibizumab injection at baseline, and subsequent injections were performed on an as-needed basis thereafter. Treatment efficacy was assessed based on best-corrected visual acuity and optical coherence tomography findings.

RESULTS: After 12 months of follow-up, the best-corrected visual acuity improved by >2 lines in 6 eyes (60%), remained within 2 lines of baseline in 3 eyes (30%), and decreased by ≥3 lines in only 1 eye (10%). The mean central foveal thickness decreased significantly from 332.2 μm at baseline to 235.7 μm at the last follow-up ($P < 0.001$), as measured by optical coherence tomography.

CONCLUSION: The preliminary results of this prospective study indicate that combination treatment with intravitreal ranibizumab injection and reduced fluence photodynamic therapy for choroidal neovascularization associated with angioid streaks seems to be effective in reducing or eliminating retinal edema, regression of neovascularization, and improving or stabilizing visual acuity without any complications. Large controlled studies are needed to evaluate the long-term effects of this combination regimen.

PMID: 21394063 [PubMed - as supplied by publisher]

Retina. 2011 Mar 9. [Epub ahead of print]

RANDOMIZED TRIAL EVALUATING SHORT-TERM EFFECTS OF INTRAVITREAL RANIBIZUMAB OR TRIAMCINOLONE ACETONIDE ON MACULAR EDEMA AFTER FOCAL/GRID LASER FOR DIABETIC MACULAR EDEMA IN EYES ALSO RECEIVING PANRETINAL PHOTOCOAGULATION.

Googe J, Brucker AJ, Bressler NM, Qin H, Aiello LP, Antoszyk A, Beck RW, Bressler SB, Ferris FL 3rd, Glassman AR, Marcus D, Stockdale CR; of the Diabetic Retinopathy Clinical Research Network.

From the *Southeastern Retina Associates, P.C., Knoxville, Tennessee; †Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania; ‡Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland; §Jaeb Center for Health Research, Tampa, Florida; Beetham Eye Institute, Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts; **Charlotte Eye Ear Nose and Throat Assoc, PA, Charlotte, North Carolina; ††National Eye Institute, National Institutes of Health, Bethesda, Maryland; and ‡‡Southeast Retina Center, P.C., Augusta, Georgia.

PURPOSE: To evaluate 14-week effects of intravitreal ranibizumab or triamcinolone in eyes receiving focal/grid laser for diabetic macular edema and panretinal photocoagulation.

METHODS: Three hundred and forty-five eyes with a visual acuity of 20/320 or better, center-involved diabetic macular edema receiving focal/grid laser, and diabetic retinopathy receiving prompt panretinal photocoagulation were randomly assigned to sham (n = 123), 0.5-mg ranibizumab (n = 113) at baseline and 4 weeks, and 4-mg triamcinolone at baseline and sham at 4 weeks (n = 109). Treatment was at investigator discretion from 14 weeks to 56 weeks.

RESULTS: Mean changes (±SD) in visual acuity letter score from baseline were significantly better in the ranibizumab (+1 ± 11; P < 0.001) and triamcinolone (+2 ± 11; P < 0.001) groups compared with those in the sham group (-4 ± 14) at the 14-week visit, mirroring retinal thickening results. These differences were not maintained when study participants were followed for 56 weeks for safety outcomes. One eye (0.9%; 95% confidence interval, 0.02%-4.7%) developed endophthalmitis after receiving ranibizumab. Cerebrovascular/cardiovascular events occurred in 4%, 7%, and 3% of the sham, ranibizumab, and triamcinolone groups, respectively.

CONCLUSION: The addition of 1 intravitreal triamcinolone injection or 2 intravitreal ranibizumab injections in eyes receiving focal/grid laser for diabetic macular edema and panretinal photocoagulation is associated with better visual acuity and decreased macular edema by 14 weeks. Whether continued long-term intravitreal treatment is beneficial cannot be determined from this study.

PMID: 21394052 [PubMed - as supplied by publisher]

Retina. 2011 Mar 3. [Epub ahead of print]

INTRAVITREAL RANIBIZUMAB COMBINED WITH VERTEPORFIN PHOTODYNAMIC THERAPY FOR TREATING POLYPOIDAL CHOROIDAL VASCULOPATHY.

Lee YH, Lee EK, Shin KS, Lee KM, Kim JY.

From the *Department of Ophthalmology, Chungnam National University, College of Medicine, Daejeon, South Korea; the †Research Institute for Medical Science, Chungnam National University, Daejeon, South Korea, and ‡Myung Eye Clinic, Seoul, South Korea.

PURPOSE: To evaluate the efficacy of intravitreal ranibizumab (Lucentis) with verteporfin photodynamic therapy for patients with polypoidal choroidal vasculopathy.

METHODS: Retrospective interventional case series. Seventeen eyes of 17 patients with symptomatic polypoidal choroidal vasculopathy who received 3 monthly intravitreal ranibizumab injections with photodynamic therapy were retrospectively reviewed. The follow-up period lasted for more than 6 months after therapy. Best-corrected visual acuity, foveal thickness determined by optical coherence tomography, and abnormal vasculature in indocyanine green angiography were evaluated.

RESULTS: The mean follow-up period was 13.8 months. The mean logarithm of the minimum angle of resolution best-corrected visual acuity was 0.43 ± 0.36 at baseline, 0.14 ± 0.24 at 6 months (P = 0.01), and 0.11 ± 0.23 at 12 months after treatment (P = 0.02). The mean foveal height was 351 ± 111 μm at baseline, 192 ± 44 μm at 6 months (P = 0.02), and 204 ± 31 μm at 12 months after treatment (P = 0.01). Patients received a mean of 3.2 ranibizumab treatments and 1.3 verteporfin photodynamic therapy treatments over the follow-up period. Re-treatment was performed in 5 of 17 eyes. The polypoidal lesions on indocyanine green angiography were regressed in six eyes, reduced in seven eyes, and unchanged in four eyes.

CONCLUSION: Intravitreal ranibizumab with photodynamic therapy may stabilize visual acuity and reduce exudative retinal detachment because of decreased vascular leaking. The combination treatment appeared to be useful for regressing polypoidal lesions on indocyanine green angiography and in reducing their recurrence.

PMID: 21386762 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2011 Mar 9. [Epub ahead of print]

Results of flexible ranibizumab treatment in age-related macular degeneration and search for parameters with impact on outcome.

Gerding H, Loukopoulos V, Riese J, Hefner L, Timmermann M.

Department of Retinology, Klinik Pallas, Louis-Giroud-Str. 20, CH-4600, Olten, Switzerland, hgerding@klinik-pallas.ch.

BACKGROUND: The aim of this study was to analyse functional results of flexible ranibizumab treatment in exudative age-related macular degeneration (AMD), and to search for parameters with impact on outcome.

METHODS: Analysis of a retrospective institutional case series (104 eyes) with a low-threshold re-treatment algorithm and monthly follow-up for 12 months.

RESULTS: Visual acuity (VA) improved at month 3 by +6.7 letters and declined slightly until month 12 to a level of +5.0 letters. On average, eyes received 5.8 injections. A significant loss in VA occurred in the whole group between months 5 and 6 (-2.0 letters), never in the "winner" group (improvement of >5 letters at month 12), between months 5 and 6 (-3.8 letters) in the "stabilizer" group (Δ of ±5 letters at month 12) and twice, between months 3 and 7 (-7.0 letters) and months 9 and 12 (-6.9 letters), in the "loser" group (loss of >5 letters at month 12). These major functional declines followed moderate but significant increases in average CFT (OCT-central foveal thickness) of 23 to 33 μm. Increased CFT followed periods with a low percentage of treated eyes per month in each group. The amount of regained vision was significantly related to the extent of previous functional loss. The critical limit of short-term VA decline that was associated with the possibility for full VA restoration can approximately be quantified at -4 letters. Restoration of short-term VA deterioration (last month) was significantly better than long-term VA loss (related to the end of loading phase). Restoration of VA loss stratifies mainly into two groups: a group that regained -25 to 25% and one that regained 75 to 125%. A significant correlation was found between the number of injections and functional outcome at month 12 for eyes receiving more than four injections. It was calculated that a mean of 8.4 injections per eye would have been necessary to stabilize vision within the first 12 months.

CONCLUSIONS: CFT is a sensitive and early predictor of VA deterioration. Four letters of acute VA loss seems to be a critical limit. VA loss of ≥4 letters appears to be associated with incomplete recovery. Eyes with <1 line of gain at the end of the loading phase should be considered for continuation of treatment at months 3 and 4. According to our calculations an average number of 8.4 injections/eye seems to be necessary to maintain stabilization of vision in the first year of treatment.

PMID: 21387180 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2011;5:37-44. Epub 2011 Jan 6.

The effect of intravitreal bevacizumab (Avastin) on ocular pulse amplitude in neovascular age-related macular degeneration.

Rechtman E, Stalmans I, Glovinsky J, Breusegem C, Moisseiev J, Van Calster J, Harris A.

Goldschleger Eye Institute, Sheba Medical Center, Ramat Gan, Israel.

PURPOSE: To evaluate the effect of intravitreal (IVT) bevacizumab in neovascular age-related macular degeneration (AMD) on global choroidal hemodynamics, as measured by ocular pulse amplitude (OPA).

METHODS: This was a two-center prospective study (Sheba Medical Center, Israel, and University Hospitals Leuven, Belgium). AMD patients who required IVT bevacizumab (1.25 mg/0.05 mL; first or repeated) were examined three times: at days 0 (prior to injection), 7 (±3), and 28 (±7) postinjection. At each visit, OPAs of both eyes were measured using the Pascal dynamic contour tonometer (DCT). A paired

t-test between preoperative and postoperative OPA was conducted. Pearson correlation was used to evaluate the influence of various measured parameters on DCT-OPA.

RESULTS: A total of 38 neovascular AMD patients were recruited, and 30 patients were included in the final analysis (18 females and 12 males; age 78.8 ± 5.82 years [mean ± standard deviation]). A good correlation was found throughout the study between the DCT-intraocular pressure (IOP) and Goldmann IOP and between DCT-IOP and DCT-OPA. No change in OPA of bevacizumab-treated eyes was found between the visits (2.24 ± 0.73, 2.2 ± 0.86, and 2.23 ± 0.73 mm Hg at visits 1, 2, and 3, respectively; paired t-test: P = 0.77 between visits 1 and 2, P = 0.98 between visits 1 and 3). No correlations were found between DCT-OPA and age, heart rate, systemic blood pressure, axial length, keratometry readings, and central corneal thickness.

CONCLUSIONS: OPA, an indirect measure of global choroidal hemodynamics, remains unchanged following IVT off-label bevacizumab. This finding adds to the growing evidence regarding the safety profile of bevacizumab in AMD treatment.

PMID: 21386919 [PubMed - in process]

Ophthalmology. 2011 Mar;118(3):600-600.e2.

Comparing ranibizumab with bevacizumab.

Biswas P, Sengupta S, Choudhary R, Home S, Paul A, Sinha S.

PMID: 21376243 [PubMed - in process]

Other treatment & diagnosis

Retina. 2011 Mar 3. [Epub ahead of print]

CHARACTERISTIC SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY FINDINGS OF MULTIFOCAL CHOROIDITIS.

Vance SK, Khan S, Klancnik JM, Freund KB.

From the *Vitreous Retina Macula Consultants of New York, New York, New York; †LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear, and Throat Hospital, New York, New York; and ‡New York University Department of Ophthalmology, New York, New York.

PURPOSE: To compare the spectral-domain optical coherence tomography (SD-OCT) findings of the acute lesions of multifocal choroiditis (MFC) with those of new-onset myopic choroidal neovascularization (CNV).

METHODS: Observational case series. A retrospective review comparing the SD-OCT findings of the acute lesions of MFC with those of early myopic CNV. Spectral-domain optical coherence tomography findings in two female patients and one male patient presenting with acute inflammatory lesions of MFC were compared with those of new-onset CNV in three patients with myopic macular degeneration. Each patient underwent a comprehensive eye examination, fundus photography, and fluorescein angiography on the initial visit. The patients underwent SD-OCT scanning at baseline and at follow-up visits using image registration and eye tracking.

RESULTS: Spectral-domain optical coherence tomography imaging of the acute lesions of MFC showed drusenlike material between the retinal pigment epithelium and the Bruch membrane, presumed vitreous cells, and localized choroidal hyperreflectivity below the subretinal pigment epithelial material. These SD-OCT findings were not usually present in the eyes with myopic CNV. The subretinal pigment epithelial material corresponded to acute lesions found on color photographs and fluorescein angiography. The subretinal pigment epithelial material and choroidal hyperreflectivity appeared to improve after treatment

with antiinflammatory or anti-vascular endothelial growth factor therapy. In contrast, SD-OCT in the patients with myopic CNV showed a very thin choroid, a posterior staphyloma, and a Type 2 (subretinal) neovascular pattern.

CONCLUSION: The acute lesions of MFC can be difficult to distinguish from myopic CNV based on clinical examination and fluorescein angiography. However, the inflammatory lesions of MFC can demonstrate characteristic SD-OCT findings not seen with myopic CNV. These SD-OCT findings may help to differentiate these two entities that typically require different treatments.

PMID: 21386760 [PubMed - as supplied by publisher]

Retina. 2011 Mar 3. [Epub ahead of print]

EFFECT OF AGING ON MACULAR FEATURES OF X-LINKED RETINOSCHISIS ASSESSED WITH OPTICAL COHERENCE TOMOGRAPHY.

Menke MN, Feke GT, Hirose T.

From the *Schepens Retina Associates Foundation, Boston, Massachusetts; †Harvard Medical School, Boston, Massachusetts; ‡Department of Ophthalmology, University of Bern, Bern, Switzerland; and §Boston Eye Group, Boston, Massachusetts.

PURPOSE: X-linked retinoschisis (XLRS) is one of the most common causes of macular degeneration in young men. The purpose of this study was to use optical coherence tomography combined with ophthalmoscopy to study the effects of aging on the morphologic changes associated with XLRS.

METHODS: Twenty-five eyes of 17 men with XLRS ranging in age from 3 years to 68 years were studied using ophthalmoscopy and optical coherence tomography. Optical coherence tomography was used to measure macular thickness and to evaluate XLRS-related structural changes. Correlation analyses between the findings and patients' age and visual acuity were performed.

RESULTS: Mean visual acuity was 20/100 (range, 20/40 to 20/400). There were no correlations between visual acuity and age or macular thickness. However, there was a significant decrease in macular thickness with age ($P < 0.01$). Eyes with posterior vitreous detachment had significantly decreased central foveal thickness ($P < 0.001$). Various retinal morphologic changes could be identified by optical coherence tomography, including epiretinal membranes, intraretinal cysts, tissue pillars bridging the schisis cavities, and tissue hyperreflectivity in collapsed XLRS. These findings were significantly correlated with age.

CONCLUSION: Optical coherence tomography revealed various retinal morphologic changes associated with XLRS. These changes were correlated with age but not with visual acuity. Younger patients showed cystic retinal elevation, whereas older patients showed collapsed retinoschisis with retinal thinning.

PMID: 21386765 [PubMed - as supplied by publisher]

Ophthalmology. 2011 Mar 7. [Epub ahead of print]

Cataract Surgery Complications in Nonagenarians.

Tseng VL, Greenberg PB, Wu WC, Jiang L, Li E, Kang JM, Scott IU, Friedmann PD.

Section of Ophthalmology, VA Medical Center, Providence, Rhode Island; Division of Ophthalmology, Warren Alpert Medical School of Brown University, Providence, Rhode Island; Research Enhancement Award Program, VA Medical Center, Providence, Rhode Island.

PURPOSE: To investigate whether nonagenarians relative to octogenarians are at increased risk of ocular complications from cataract surgery in the US Veterans Health Administration (VHA).

DESIGN: A retrospective cohort study.

PARTICIPANTS: A total of 554 nonagenarians and 11 407 octogenarians who received cataract surgery in the VHA.

METHODS: Nonagenarians and octogenarians who received 1 cataract surgery without a second surgery within 90 days between October 1, 2005, and September 30, 2007, were identified using the National Patient Care Database (NPCD). Data collected include demographics, preoperative systemic and ocular comorbidities, intraoperative complications, and 90-day postoperative complications. The adjusted odds ratio (OR) of complications in nonagenarians using octogenarians as a reference group was calculated using logistic regression modeling.

MAIN OUTCOME MEASURES: Intraoperative and postoperative ocular complications within 90 days of cataract surgery in nonagenarians versus octogenarians.

RESULTS: The most common systemic comorbidity for both age groups was diabetes mellitus (DM), and the most common ocular comorbidity for both age groups was age-related macular degeneration (AMD). Octogenarians had a higher prevalence of most systemic comorbidities, and nonagenarians had a higher prevalence of most ocular comorbidities. The most common intraoperative and postoperative complications for both age groups were vitreous loss or posterior capsular tear and posterior capsular opacification. The risk of having any intraoperative or postoperative complication was 13.5% for octogenarians and 13.4% for nonagenarians (P = 0.9001). The OR of having any intraoperative or postoperative complication in nonagenarians with octogenarians as a reference group was 0.94 (95% confidence interval, 0.73-1.22).

CONCLUSIONS: Nonagenarians relative to octogenarians are not at increased risk of ocular complications from cataract surgery in the VHA. Further studies are needed to evaluate other outcome parameters, such as visual function and quality of life, in nonagenarians undergoing cataract surgery.

PMID: 21388686 [PubMed - as supplied by publisher]

Ophthalmic Res. 2011 Mar 8;46(3):152-159. [Epub ahead of print]

Spectral-Domain versus Time Domain Optical Coherence Tomography before and after Ranibizumab for Age-Related Macular Degeneration.

Querques G, Forte R, Berboucha E, Martinelli D, Coscas G, Soubrane G, Souied EH.

Department of Ophthalmology, Centre Hospitalier Intercommunal de Créteil, University Paris XII, Créteil, France.

Purpose: To study the ability to appreciate qualitative features that indicate disease activity in patients with neovascular age-related macular degeneration (AMD) and to analyze the differences in automated retinal thickness measurement, using 1 time domain optical coherence tomography (TD-OCT) and 2 different spectral-domain OCT (SD-OCT) machines.

Methods: Thirty-three consecutive naïve patients with neovascular AMD underwent Stratus TD-OCT, Cirrus SD-OCT and Spectralis SD-OCT, at baseline, 1 h, 1 day, 1 week and 1 month after intravitreal ranibizumab injection.

Results: As regards the ability to detect retinal cysts, subretinal fluid and pigment epithelium detachment, at each follow-up visit, there was a significant correlation among all 3 OCT devices ($p < 0.05$), even though Cirrus SD-OCT and Spectralis SD-OCT showed the highest level of intermachine agreement. At each follow-up visit, automated retinal thickness measurements showed a greater mean central macular thickness (CMT) for both Spectralis SD-OCT and Cirrus SD-OCT, compared with Stratus TD-OCT. However, the mean paired differences in CMT among the 3 OCT devices were not statistically significant ($p > 0.05$). Overall, Cirrus SD-CT showed fewer segmentation errors, compared with both Spectralis SD-OCT and Stratus TD-OCT.

Conclusion: SD-OCT showed a greater ability to evaluate qualitative features indicating disease activity and fewer errors in automated segmentation. However, differences in CMT changes were similar between TD-OCT and SD-OCT systems during follow-up.

PMID: 21389740 [PubMed - as supplied by publisher]

Ophthalmology. 2011 Mar 7. [Epub ahead of print]

Spectral Domain Optical Coherence Tomography Imaging of Drusen in Nonexudative Age-Related Macular Degeneration.

Gregori G, Wang F, Rosenfeld PJ, Yehoshua Z, Gregori NZ, Lujan BJ, Puliafito CA, Feuer WJ.

PURPOSE: To measure drusen area and volume in eyes with nonexudative age-related macular degeneration (AMD) using spectral domain optical coherence tomography imaging (SD-OCT).

DESIGN: Evaluation of diagnostic technology.

PARTICIPANTS: One hundred three eyes from 74 patients with drusen.

METHODS: Patients with drusen secondary to nonexudative AMD were enrolled in this study. Five separate SD-OCT scans, each consisting of 40 000 uniformly spaced A-scans organized as 200 A-scans in each B-scan and 200 horizontal B-scans, were performed on each eye. Each scan covered a retinal area of 6 × 6 mm centered on the fovea. A novel algorithm was used to quantitatively assess drusen area and volume. Measurements from the entire scans, as well as in regions contained within 3- and 5-mm circles centered on the fovea, were analyzed. Test-retest standard deviations of drusen area and volume measurements were calculated for each eye.

MAIN OUTCOME MEASURES: Drusen area and volume.

RESULTS: The algorithm created drusen maps that permitted both qualitative and quantitative assessment of drusen area and volume. Both the qualitative appearance and the quantitative measurements of drusen area and volume were highly reproducible over the 5 different datasets. The intraclass correlation coefficient was >0.99 for both area and volume measurements on the entire dataset as well as the 3- and 5 -mm circles. The correlation between lesion size and the test-retest standard deviations can be eliminated by performing a square root transformation of the area measurements and a cube root transformation of the volume measurements. These transformed data allowed for the inclusion of all drusen sizes in the calculation of an estimated single pooled test-retest standard deviation, which will be useful for longitudinal studies of drusen natural history.

CONCLUSIONS: A novel algorithm for the qualitative and quantitative assessment of drusen imaged using SD-OCT was shown to be highly reproducible. The ability to assess drusen volume reliably represents a new quantitative parameter to measure in AMD and may be useful when assessing disease progression, particularly in trials for treatments of nonexudative AMD.

PMID: 21388687 [PubMed - as supplied by publisher]

Pathogenesis & epidemiolology

Eye (Lond). 2011 Mar 11. [Epub ahead of print]

Complement in age-related macular degeneration: a focus on function.

Bradley DT, Zipfel PF, Hughes AE.

Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University

Belfast, Belfast, UK.

Abstract

Age-related macular degeneration (AMD) is an inflammatory disease, which causes visual impairment and blindness in older people. The proteins of the complement system are central to the development of this disease. Local and systemic inflammation in AMD are mediated by the deregulated action of the alternative pathway of the complement system. Variants in complement system genes alter an individual's risk of developing AMD. Recent studies have shown how some risk-associated genetic variants alter the function of the complement system. In this review, we describe the evolution of the complement system and bring together recent research to form a picture of how changes in complement system genes and proteins affect the function of the complement cascade, and how this affects the development of AMD. We discuss the application of this knowledge to prevention and possible future treatments of AMD.Eye advance online publication, 11 March 2011; doi:10.1038/eye.2011.37.

PMID: 21394116 [PubMed - as supplied by publisher]

PLoS One. 2011 Feb 28;6(2):e16722.

Cigarette Smoke-Related Hydroquinone Dysregulates MCP-1, VEGF and PEDF Expression in Retinal Pigment Epithelium in Vitro and in Vivo.

Pons M, Marin-Castaño ME.

Department of Ophthalmology, Miller School of Medicine, Bascom Palmer Eye Institute, University of Miami, Miami, Florida, United States of America.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of legal blindness in the elderly population. Debris (termed drusen) below the retinal pigment epithelium (RPE) have been recognized as a risk factor for dry AMD and its progression to wet AMD, which is characterized by choroidal neovascularization (CNV). The underlying mechanism of how drusen might elicit CNV remains undefined. Cigarette smoking, oxidative damage to the RPE and inflammation are postulated to be involved in the pathophysiology of the disease. To better understand the cellular mechanism(s) linking oxidative stress and inflammation to AMD, we examined the expression of pro-inflammatory monocyte chemoattractant protein-1 (MCP-1), pro-angiogenic vascular endothelial growth factor (VEGF) and anti-angiogenic pigment epithelial derived factor (PEDF) in RPE from smoker patients with AMD. We also evaluated the effects of hydroquinone (HQ), a major pro-oxidant in cigarette smoke on MCP-1, VEGF and PEDF expression in cultured ARPE-19 cells and RPE/choroids from C57BL/6 mice.

PRINCIPAL FINDINGS: MCP-1, VEGF and PEDF expression was examined by real-time PCR, Western blot, and ELISA. Low levels of MCP-1 protein were detected in RPE from AMD smoker patients relative to controls. Both MCP-1 mRNA and protein were downregulated in ARPE-19 cells and RPE/choroids from C57BL/6 mice after 5 days and 3 weeks of exposure to HQ-induced oxidative injury. VEGF protein expression was increased and PEDF protein expression was decreased in RPE from smoker patients with AMD versus controls resulting in increased VEGF/PEDF ratio. Treatment with HQ for 5 days and 3 weeks increased the VEGF/PEDF ratio in vitro and in vivo.

CONCLUSION: We propose that impaired RPE-derived MCP-1-mediated scavenging macrophages recruitment and phagocytosis might lead to incomplete clearance of proinflammatory debris and infiltration of proangiogenic macrophages which along with increased VEGF/PEDF ratio favoring angiogenesis might promote drusen accumulation and progression to CNV in smoker patients with dry AMD.

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Toll-like receptor 3 is required for development of retinopathy caused by impaired all-trans-retinal clearance in mice.

Shiose S, Chen Y, Okano K, Roy S, Kohno H, Tang J, Pearlman E, Maeda T, Palczewski K, Maeda A.

Case Western Reserve University, United States.

Abstract

Chronic inflammation is an important component that contributes to many age-related neurodegenerative diseases including macular degeneration. Here we report a role for toll-like receptor 3 (TLR3) in cone-rod dystrophy (CORD) of mice lacking ATP-binding cassette transporter 4 (Abca4) and retinol dehydrogenase 8 (Rdh8), proteins critical for all-trans-retinal clearance in the retina. Increased expression of TLR-signaling elements and inflammatory changes were observed in Rdh8-/-Abca4-/- eyes by RNA expression analysis. Unlike 3-month-old Rdh8-/-Abca4-/- mice that developed CORD, 6-month-old Tlr3-/-Rdh8-/-Abca4-/- mice did not evidence an abnormal retinal phenotype. Light-induced retinal degeneration in Tlr3-/-Rdh8-/-Abca4-/- mice was milder than that in Rdh8-/-Abca4-/- mice, and a 2-fold increased Tlr3 expression was detected in light-illuminated retinas of Rdh8-/-Abca4-/- mice compared to non-illuminated retinas. Poly(I:C), a TLR3 ligand, can cause caspase-8-independent cellular apoptosis. Whereas poly(I:C) induced retinal cell death in Rdh8-/-Abca4-/- and WT mice both in vivo and ex vivo, this was not seen in mice lacking Tlr3. Far fewer invasive macrophage/microglial cells in the subretinal space and weaker activation of Muller glial cells were exhibited by Tlr3-/-Rdh8-/-Abca4-/- mice compared to Rdh8-/-Abca4-/- mice at 3- and 6-months of age, indicating that loss of Tlr3 inhibits local inflammation in the retina. Both poly(I:C) and endogenous products emanating from dying/dead retinal cells induced NF-κB and IRF3 activation. These findings demonstrate that endogenous products from degenerating retina stimulate TLR3 that causes cellular apoptosis and retinal inflammation, and that loss of TLR3 protects mice from CORD.

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Prevalence and causes of registered blindness in the largest federal state of Germany.

Finger RP, Fimmers R, Holz FG, Scholl HP.

University of Bonn, Bonn, Germany.

Aim: As no current estimates for the prevalence and causes of blindness in Germany are available, the database of Germany's largest welfare institution (covering 9.5 million people in the federal state of Northrhine) assessing eligibility for an allowance payable to blind people was used to investigate the prevalence and the specific causes of blindness and visual impairment.

Methods: Data from a representative sample of 5100 cases out of 20 365 cases were extracted, entered into an electronic database and statistically analysed. Blindness and severe vision impairment were defined as visual acuity equal to or below 20/1000 and 20/400, respectively, in the better-seeing eye.

Results: The mean age of the overall sample was 72±22 years and the mean visual acuity of the better seeing eye was 20/800. The prevalence of blindness and severe vision impairment in Northrhine was estimated to be 47.91 per 100 000 persons. Most registered visual impairment was due to age-related macular degeneration (AMD; 41%), followed by glaucoma (15%) and diabetic eye disease (10%). Sixty-five per cent of registered blind people were women, 56% of them over the age of 80 years. Registered children and teenagers had the relative worst visual acuity (hand movement) and patients with retinal dystrophies had the relative best visual acuity (20/200) within the whole cohort (p<0.001). Standardised prevalence of blindness and severe visual impairment for Germany is estimated to be 44.4/100.000 (57.94 for women and 30.78 for men).

Conclusions: Prevalence of blindness and severe vision impairment for Germany compare well to other European countries. AMD is the most prevalent cause of registered blindness and severe vision impairment, and prevalence in women is higher. Generally, prevalence increases with age. Provision of support and welfare services need to be organised accordingly.

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Animal models of retinal disease.

Fletcher EL, Jobling AI, Vessey KA, Luu C, Guymer RH, Baird PN.

Department of Anatomy and Cell Biology, The University of Melbourne, Parkville, Victoria, Australia.

Abstract

Diseases of the retina are the leading causes of blindness in the industrialized world. The recognition that animals develop retinal diseases with similar traits to humans has led to not only a dramatic improvement in our understanding of the pathogenesis of retinal disease but also provided a means for testing possible treatment regimes and successful gene therapy trials. With the advent of genetic and molecular biological tools, the association between specific gene mutations and retinal signs has been made. Animals carrying natural mutations usually in one gene now provide well-established models for a host of inherited retinal diseases, including retinitis pigmentosa, Leber congenital amaurosis, inherited macular degeneration, and optic nerve diseases. In addition, the development of transgenic technologies has provided a means by which to study the effects of these and novel induced mutations on retinal structure and function. Despite these advances, there is a paucity of suitable animal models for complex diseases, including age-related macular degeneration (AMD) and diabetic retinopathy, largely because these diseases are not caused by single gene defects, but involve complex genetics and/or exacerbation through environmental factors, epigenetic, or other modes of genetic influence. In this review, we outline in detail the available animal models for inherited retinal diseases and how this information has furthered our understanding of retinal diseases. We also examine how transgenic technologies have helped to develop our understanding of the role of isolated genes or pathways in complex diseases like AMD, diabetes, and glaucoma.

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Genetics

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Simple strategies for haplotype analysis of the X chromosome with application to age-related macular degeneration.

Jiang R, Dong J, Joo J, Geller NL, Zheng G.

Department of Mathematical Sciences, Michigan Technological University, Houghton, MI, USA.

Abstract

For haplotype analysis of the X chromosome, haplotype-sharing (HS) statistics with sliding windows are defined for males and females separately, which are then combined to a single HS test for the X chromosome. When independent replication samples are not available, the training-testing sets approach is used to validate this procedure and a permutation method is used to obtain its P-value. We applied this method to the X chromosome (with 1804 SNPs) for age-related macular degeneration (AMD). We found a window of five SNPs over a 272 kb region associated with AMD after Bonferroni correction. An examination of the odds ratio and the population attributable risks revealed a disease-preventive haplotype, ATGAC, on

these five SNPs. For elderly females without this haplotype, the likelihood of AMD is increased by a factor of 4.75 with a 95% confidence interval (1.43, 15.82). The frequency of ATGAC in HapMap CEU is 0.276. These five SNPs are covered by the gene DIAPH2, which is known to cause premature ovarian failure (POF) in females. Our results indicated that DIAPH2 may be a polygenic pleiotropy for POF and AMD.European Journal of Human Genetics advance online publication, 9 March 2011; doi:10.1038/ejhg.2011.35.

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Elastin rs2301995 Polymorphism is not Associated with Polypoidal Choroidal Vasculopathy in Caucasians.

Lima LH, Merriam JE, Freund KB, Barbazetto IA, Spaide RF, Yannuzzi LA, Allikmets R.

Vitreous, Retina, Macula Consultants of New York and the LuEsther T. Mertz Retina Research Center, Manhattan Eye, Ear, and Throat Hospital, New York.

Purpose: To investigate the association of the rs2301995 haplotype-tagging single nucleotide polymorphism (htSNP) in the elastin gene (ELN) with polypoidal choroidal vasculopathy (PCV) in European -American patients.

Methods: Association analysis of allele and genotype frequencies, determined by TaqMan assays, was performed for the rs2301995 haplotype-tagging single nucleotide polymorphism (htSNP) in the ELN locus in fifty-six patients with PCV, 368 patients with advanced age-related macular degeneration (AMD) and 368 age- and ethnically-matched unaffected controls.

Results: The ELN rs2301995 SNP was not statistically significantly associated with the PCV phenotype ($P = 0.9$). The frequency of the minor allele of the rs2301995 SNP was practically identical in the PCV, AMD and control groups (6.3% vs. 5.4% vs. 7.1%).

Conclusion: The PCV phenotype in European-American patients is not associated with rs2301995 SNP in the ELN locus.

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Age-related macular degeneration genetics.

* Letter

Byeon SH, Chu YK.

Seoul, Korea.

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