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MD Research News

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Drug treatment

Ophthalmology. 2011 Apr;118(4):663-71.

Safety and Efficacy of a Flexible Dosing Regimen of Ranibizumab in Neovascular Age-Related Macular Degeneration: The SUSTAIN Study.

Holz FG, Amoaku W, Donate J, Guymer RH, Kellner U, Schlingemann RO, Weichselberger A, Staurenghi G; SUSTAIN Study Group.

Department of Ophthalmology, University of Bonn, Bonn, Germany.

OBJECTIVE: To evaluate the safety and efficacy of individualized ranibizumab treatment in patients with neovascular age-related macular degeneration.

DESIGN: Twelve-month, phase III, multicenter, open-label, single-arm study.

PARTICIPANTS: A total of 513 ranibizumab-naïve SUSTAIN patients.

INTERVENTION: Three initial monthly injections of ranibizumab (0.3 mg) and thereafter pro re nata (PRN) retreatment for 9 months based on prespecified retreatment criteria. Patients switched to 0.5 mg ranibizumab after approval in Europe.

MAIN OUTCOME MEASURES: Frequency of adverse events (AEs), monthly change of best-corrected visual acuity (BCVA) and central retinal thickness (CRT) from baseline, the time to first re-treatment, and the number of treatments were assessed.

RESULTS: A total of 249 patients (48.5%) reported ocular AEs, and 8 (1.5%) deaths, 5 (1.2%) patients with ocular serious AEs of the study eye (retinal hemorrhage, cataract, retinal pigment epithelial tear, reduced visual acuity [VA], vitreous hemorrhage), and 19 (3.7%) patients with arteriothromboembolic events were observed. Most frequent AEs in the study eye were reduced VA (18.5%), retinal hemorrhage (7.2%), increased intraocular pressure (7.0%), and conjunctival hemorrhage (5.5%). The average number of re-treatments from months 3 to 11 was 2.7. Mean best-corrected visual acuity increased steadily from baseline to month 3 to reach +5.8 letters, decreased slightly from month 3 to 6, and remained stable from month 6 to 12, reaching +3.6 at month 12. Mean change in CRT was -101.1 μm from baseline to month 3 and -91.5 μm from baseline to month 12.

CONCLUSIONS: The safety results are comparable to the favorable tolerability profile of ranibizumab observed in previous pivotal clinical studies; individualized treatment with less than monthly re-treatments shows a similar safety profile as observed in previous randomized clinical trials with monthly ranibizumab treatment. Efficacy outcomes were achieved with a low average number of re-treatments. Visual acuity in SUSTAIN patients with individualized re-treatment based on VA/optical coherence tomography assessment

reached on average a maximum after the first 3 monthly injections, decreased slightly under PRN during the next 2 to 3 months, and was then sustained throughout the treatment period.

PMID: 21459217 [PubMed - in process]

Ophthalmology. 2011 Apr;118(4):615-25.

The RESTORE Study Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema.

Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, Sutter F, Simader C, Burian G, Gerstner O, Weichselberger A; RESTORE study group.

Centre for Vision Research (Westmead Millennium Institute), University of Sydney, Sydney, Australia.

OBJECTIVE: To demonstrate superiority of ranibizumab 0.5 mg monotherapy or combined with laser over laser alone based on mean average change in best-corrected visual acuity (BCVA) over 12 months in diabetic macular edema (DME).

DESIGN: A 12-month, randomized, double-masked, multicenter, laser-controlled phase III study.

PARTICIPANTS: We included 345 patients aged ≥18 years, with type 1 or 2 diabetes mellitus and visual impairment due to DME.

METHODS: Patients were randomized to ranibizumab + sham laser (n = 116), ranibizumab + laser (n = 118), or sham injections + laser (n = 111). Ranibizumab/sham was given for 3 months then pro re nata (PRN); laser/sham laser was given at baseline then PRN (patients had scheduled monthly visits).

MAIN OUTCOME MEASURES: Mean average change in BCVA from baseline to month 1 through 12 and safety.

RESULTS: Ranibizumab alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12 (+6.1 and +5.9 vs +0.8; both P<0.0001). At month 12, a significantly greater proportion of patients had a BCVA letter score ≥15 and BCVA letter score level >73 (20/40 Snellen equivalent) with ranibizumab (22.6% and 53%, respectively) and ranibizumab + laser (22.9% and 44.9%) versus laser (8.2% and 23.6%). The mean central retinal thickness was significantly reduced from baseline with ranibizumab (-118.7 μm) and ranibizumab + laser (-128.3 μm) versus laser (-61.3 μm; both P<0.001). Health-related quality of life, assessed through National Eye Institute Visual Function Questionnaire (NEI VFQ-25), improved significantly from baseline with ranibizumab alone and combined with laser (P<0.05 for composite score and vision-related subscales) versus laser. Patients received ~7 (mean) ranibizumab/sham injections over 12 months. No endophthalmitis cases occurred. Increased intraocular pressure was reported for 1 patient each in the ranibizumab arms. Ranibizumab monotherapy or combined with laser was not associated with an increased risk of cardiovascular or cerebrovascular events in this study.

CONCLUSIONS: Ranibizumab monotherapy and combined with laser provided superior visual acuity gain over standard laser in patients with visual impairment due to DME. Visual acuity gains were associated with significant gains in VFQ-25 scores. At 1 year, no differences were detected between the ranibizumab and ranibizumab + laser arms. Ranibizumab monotherapy and combined with laser had a safety profile in DME similar to that in age-related macular degeneration.

PMID: 21459215 [PubMed - in process]

Ophthalmology. 2011 Apr;118(4):609-14.

Expanded 2-Year Follow-up of Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema.

Diabetic Retinopathy Clinical Research Network; Writing Committee, Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL 3rd, Friedman SM, Glassman AR, Scott IU, Stockdale CR, Sun JK.

Elman Retina Group, PA, Baltimore, Maryland.

OBJECTIVE: To report expanded 2-year follow-up of a previously reported randomized trial evaluating intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for treatment of diabetic macular edema (DME).

DESIGN: Multicenter, randomized clinical trial.

PARTICIPANTS: A total of 854 study eyes of 691 participants with visual acuity of 20/32 to 20/320 (approximate Snellen equivalent) and DME involving the fovea.

METHODS: Continuation of procedures previously reported for the randomized trial.

MAIN OUTCOME MEASURES: Best-corrected visual acuity and safety at the 2-year visit.

RESULTS: At the 2-year visit, compared with the sham + prompt laser group, the mean change in the visual acuity letter score from baseline was 3.7 letters greater in the ranibizumab + prompt laser group (95% confidence interval adjusted for multiple comparisons [aCI], -0.4 to +7.7), 5.8 letters greater in the ranibizumab + deferred laser group (95% aCI, +1.9 to +9.8), and 1.5 letters worse in the triamcinolone + prompt laser group (95% aCI, -5.5 to +2.4). After the 1- to 2-year visit in the ranibizumab + prompt or deferred laser groups, the median numbers of injections were 2 and 3 (potential maximum of 13), respectively. At the 2-year visit, the percentages of eyes with central subfield thickness ≥250 μm were 59% in the sham + prompt laser group, 43% in the ranibizumab + prompt laser group, 42% in the ranibizumab + deferred laser group, and 52% in the triamcinolone + prompt laser group. No systemic events attributable to study treatment were apparent. Three eyes in 3 (0.8%) of 375 participants had injection-related endophthalmitis in the ranibizumab groups, whereas elevated intraocular pressure and cataract surgery were more frequent in the triamcinolone + prompt laser group.

CONCLUSIONS: The expanded 2-year results reported are similar to results published previously and reinforce the conclusions originally reported: Ranibizumab should be considered for patients with DME and characteristics similar to those of the cohort in this clinical trial, including vision impairment with DME involving the center of the macula.

PMID: 21459214 [PubMed - in process]

Semin Ophthalmol. 2011 Mar;26(2):61-3.

Effect of Reflux of Drug During Intravitreal Anti-VEGF Therapies on Foveal Thickness.

Saeed MU, Qureshi F, Batra R, Clark D.

Department of Ophthalmology, Aintree University Hospitals NHS Trust, Liverpool, UK.

Purpose: To report any variation in foveal thickness in eyes with and without reflux during anti-VEGF injection.

Method: Review of electronic case notes and scans.

Results: 18 patients receiving bevazicumab were identified as having reflux (n = 3) or no reflux (n = 15). Pre-injection average central foveal thickness (CFT) was 439 microns (μ) and post-injection average CFT was

417µ. The change in mean CFT was -22 µ (range -330 to 336 µ). 70 patients receiving ranibizumab (lucentis) were identified as having reflux (n = 22) or no reflux (n = 48). Average pre-injection CFT was 336 µ and post-injection average CFT was 289 µ. The change in mean CFT was -48 µ (range -163 to 443 µ). The change in CFT between the group with reflux and no reflux in bevazicumab and ranibizumab injections was statistically insignificant.

Conclusion: Reflux following injection of anti-VEGF agents does not appear to cause a sub-therapeutic effect.

PMID: 21469967 [PubMed - in process]

Semin Ophthalmol. 2011 Mar;26(2):52-4.

Primary intravitreal ranibizumab for myopic choroidial neovascularisation.

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Abstract

Myopic chorodial neovascularisation (mCNV) is an important cause of visual loss in high myopia with almost 10% of eyes with pathological myopia developing mCNV. Intravitreal anti-VEGF agents have recently been documented to be effective in mCNV. However, controversy exists regarding the optimal drug, its dose, and the frequency of administration. We performed a retrospective case review examining patients who had myopia of less than -6D and a chorodial neovascular membrane diagnosed on fundus fluorescein angiography (FFA) that were treated with 3 injections of ranibizumab (Lucentis) 5mg/0.05ml given at monthly intervals. The course was repeated if the ocular coherence tomography (OCT) continued to show intra-retinal oedema at review. We recorded logMAR visual acuities and central foveal thickness (CFT) at baseline and final review. Improvement in visual acuity was significantly improved (p = 0.049) by a mean of 0.24 logMAR (range 0 to 0.74). Every patient achieved at least visual stability. Mean CFT reduction was also significantly improved (p = 0.02) by a mean of 109 microns (range -8 to 198). Our series and current literature seem to support as primary treatment a standard dose of an anti-VEGF agent. Further, larger studies are required to clarify whether any particular injection strategy is clearly superior.

PMID: 21469965 [PubMed - in process]

Klin Monbl Augenheilkd. 2011 Apr 6. [Epub ahead of print]

Results of an Expert Survey on VEGF Inhibitors in Ophthalmology.

[Article in German]

Kühn T.

ContraCare GmbH, Fürth.

BACKGROUND: VEGF inhibition is an important treatment option for patients with eye diseases like wet AMD or diabetic eye diseases. Concerning VEGF inhibition in Germany's ophthalmology there is lack of health-care data.

METHODOLOGY: A standardised telephone survey addressing treating ophthalmologists in Germany was used to acquire information in terms of VEGF inhibitors in ophthalmology.

RESULTS: 44.9 % considered ranibizumab (Lucentis®) and bevacizumab (Avastin®) as equal regarding efficacy and safety. Even so ranibizumab captured with 69.8 % regarding patients under treatment the

greatest market share. 26.1 % estimated that less than 10 % of patients with diabetic eye diseases are under treatment while 23.4 % assumed that at present all treatable patients are under treatment. The integration of IVI into the EBM is recommended by only 9.4 %. Using the content of one vial for the treatment of more than one patient is challenged by 66.4 % of all participating ophthalmologists. 50.7 % of these would accept the splitting procedure on condition that proof of drug quality in terms of efficacy and safety is given.

DISCUSSION: The dominance of ranibizumab is based upon a forensic discussion about off-label use of drugs and liability of the treating physicians. In this connection it should not be forgotten that at the end of 2009 the approval of pegaptanib (Macugen®) and ranibizumab covers exclusively the indication "neovascular AMD". Since Novartis gained new indication for Lucentis in EU for vision loss due to diabetic macular edema (DME) it is to be expected that VEGF inhibition will become first line for patients with DME. The cost effectiveness of the anti-VEGF therapy in ophthalmology is based upon the treatment of several patients with one drug package. The integration of IVI into the EBM is not recommended by the majority of Germany's ophthalmologists because neither would the patients benefit nor would the health-care data transparency increase.

CONCLUSION: To evaluate the ophthalmological anti-VEGF market in Germany and to identify and secure the treatment quality a recurring acquisition of health-care data with following management actions is needed.

PMID: 21472638 [PubMed - as supplied by publisher]

Curr Vasc Pharmacol. 2011 Apr 6. [Epub ahead of print]

Systemic Adverse Drug Reactions Secondary to Anti-VEGF Intravitreal Injection in Patients with Neovascular Age-Related Macular Degeneration.

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Abstract

The wet form of age related macular degeneration (AMD), known also as exudative or neovascular, is characterized by the formation of a pathological choroidal neovascular membrane (CNV) responsible for most cases of severe blindness. Vascular endothelial growth factor (VEGF) is a homodimeric glycoprotein acting as a growth factor selective for endothelial cells; it regulates angiogenesis and enhances vascular permeability and plays a leading role in this disorder. The consistent association between CNV and increased VEGF-A expression provides a strong reason for exploring the therapeutic potential of anti-VEGF agents in the treatment of neovascular AMD. The importance of VEGF for the development of AMD-related CNV has led to the development of a strategy able to block its pathologic effects. The rationale is that a blockade of VEGF actions could be effective in arresting choroidal angiogenesis and also reducing the vascular permeability, which is frequently the main cause of visual acuity deterioration. However, VEGF has also important functions in vascular physiology. The effects of anti-VEGF therapy may inhibit these functions. Herein we report the systemic adverse events secondary to intravitreal administration of these compounds i.e. the main cardiovascular effects (thrombosis, hemorrhage, hypertension, proteinuria), as well as the less frequent cerebrovascular accidents, myocardial infarction, transient ischemic attacks, deep vein thrombosis, pulmonary embolism and thrombophlebitis.

PMID: 21470108 [PubMed - as supplied by publisher]

Case Report Ophthalmol. 2011 Feb 12;2(1):59-64.

Central serous chorioretinopathy with subretinal deposition of fibrin-like material and its prompt response to ranibizumab injections.

Symeonidis C, Kaprinis K, Manthos K, Androudi S, Anastassilakis K, Dimitrakos SA.

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PURPOSE: Central serous chorioretinopathy (CSCR) manifests as neurosensory detachment of the macula and can be attributed to focal or multifocal leakage in the retinal pigment epithelium (RPE). Fibrin accumulation in the subretinal space is an unusual and heretofore unreported visually damaging manifestation of severe CSCR.

METHODS: The patient was followed up with the use of biomicroscopy, fluorescein angiography, and optical coherence tomography (OCT).

RESULTS: A 32-year-old woman was referred to our department complaining of metamorphopsia and decreased visual acuity in the right eye. Best-corrected visual acuity (BCVA) was 20/40 in the right eye and 20/20 in the left eye. Biomicroscopy revealed an irregularly shaped foveal elevation and wrinkling in the right eye. OCT showed a steep neurosensory retina elevation with a highly reflective material accumulation in the subretinal space, presumably fibrin. Our diagnosis was CSCR complicated by subretinal fibrin accumulation. Since most of these cases resolve spontaneously, the patient was kept under observation; 1 month later, the fibrin accumulation had expanded subfoveally (BCVA 20/200). The patient was offered 3 intravitreal ranibizumab injections. After the initial injection, BCVA improved to 20/50 and, after the 3 injections, to 20/30. Two months later (BCVA 20/30), fresh leakage was observed at the margin of the original lesion, and an additional intravitreal ranibizumab injection was performed. After another 2 months, BCVA stabilized at 20/25 and remained stable throughout the 12 months after the initial injection.

CONCLUSIONS: Prompt recognition of CSCR complicated by subretinal fibrin and immediate intervention may result in recovery from this potentially devastating complication. Ranibizumab may be an alternative treatment option in the management of refractory CSCR complicated by subretinal fibrin accumulation.

PMID: 21475646 [PubMed - in process]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2011 Apr 1. [Epub ahead of print]

Comparison of fetal RPE and human embryonic stem cell derived-RPE (hES-RPE) behavior on aged human Bruch's membrane.

Sugino IK, Sun Q, Wang J, Nunes CF, Cheewatrakoolpong N, Rapista A, Johnson AC, Malcuit C, Klimanskaya I, Lanza R, Zarbin MA.

The Institute of Ophthalmology and Visual Science, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ.

Purpose: Compare hES-RPE and fetal RPE (fRPE) behavior on human Bruch's membrane (BM) from aged and age-related macular degeneration (AMD) donors.

Methods. hES-RPE of 3 degrees of pigmentation and fRPE were cultured on BM explants. Explants were assessed by light, confocal, and scanning electron microscopy. Integrin mRNA levels were determined by real-time PCR. Secreted proteins in media were analyzed by multiplex protein analysis after 48 hour exposure at culture day 21.

Results. hES-RPE showed impaired initial attachment compared to fRPE; pigmented hES-RPE showed

nuclear densities similar to fRPE at day 21. At days 3 and 7, hES-RPE resurfaced BM to a limited degree, showed little proliferation (Ki-67), and partial retention of RPE markers (MITF, cytokeratin, CRALBP). TUNEL-positive nuclei were abundant at day 3. fRPE exhibited substantial BM resurfacing at day 3 with decreased resurfacing at later times. Most fRPE retained RPE markers. Ki-67-positive nuclei decreased with time in culture. TUNEL staining was variable. Increased integrin mRNA expression did not appear to affect cell survival at day 21. hES-RPE and fRPE protein secretion was similar on equatorial BM except for higher levels of NGF and TSP2 by hES-RPE. On submacular BM, fRPE secreted more VEGF, BDNF, and PDGF; hES-RPE secreted more TSP2.

Conclusions. Although pigmented hES-RPE and fRPE resurfaced aged and AMD BM to a similar, limited degree at day 21, cell behavior at earlier times was markedly dissimilar. Differences in protein secretion may indicate that hES-RPE may not function identically to native RPE after seeding on aged or AMD BM.

PMID: 21460262 [PubMed - as supplied by publisher]

Ophthalmology. 2011 Apr 2. [Epub ahead of print]

Vitreoretinal Interface and Foveal Deformation in Asymptomatic Fellow Eyes of Patients with Unilateral Macular Holes.

Kumagai K, Hangai M, Larson E, Ogino N.

Shinjo Ophthalmologic Institute, Miyazaki, Japan.

PURPOSE: To compare the vitreoretinal interface of the asymptomatic fellow eyes of patients with unilateral macular holes (MHs) with that of the asymptomatic fellow eyes of patients with other retinal diseases and with that of healthy eyes.

DESIGN: Retrospective, observational cross-sectional study.

PARTICIPANTS: This study included 137 healthy volunteers and 929 eyes of 929 patients with various unilateral retinal diseases.

METHODS: We reviewed medical charts, fundus photographs, and spectral-domain optical coherence tomographic (SD OCT) images. The incidence of the features of the vitreoretinal interface and foveal structures in the SD OCT images were compared among the asymptomatic fellow eyes of patients with unilateral MHs (n = 242), age-related macular degeneration (n = 129), epiretinal membrane (n = 185), macular pseudohole (n = 48), rhegmatogenous retinal detachment (n = 68), retinal vein occlusion (n = 257), and 1 of the eyes of healthy individuals (n = 137).

MAIN OUTCOME MEASURES: Findings of slit-lamp biomicroscopy and SD OCT B-scan images.

RESULTS: The SD OCT B-scan images showed different types of foveal deformations associated with vitreofoveal adhesions in eyes without a posterior vitreous detachment (PVD) in the macular area. The incidence of the foveal deformations associated with vitreofoveal adhesions was significantly higher ($P<0.0001$) in the fellow eyes of the unilateral MH group (17%) than that in the other groups (0%-2%), except for the macular pseudohole group (8%). The SD OCT B-scan images also showed residual foveal deformations in eyes with a macular PVD. The incidence of a residual foveal deformation in eyes with a macular PVD was significantly higher ($P<0.0001$) in the MH group (32%) than that in any other group (0%-9%).

CONCLUSIONS: The higher incidence of foveal deformations in the fellow eyes of patients with unilateral MHs with and without vitreofoveal adhesions suggests that patients in whom MHs develop have abnormally strong vitreofoveal adhesions sufficient to cause foveal deformation.

PMID: 21459450 [PubMed - as supplied by publisher]

Optom Vis Sci. 2011 Mar 31. [Epub ahead of print]

Smoking Cessation Referrals in Optometric Practice: A Canadian Pilot Study.

Kennedy RD, Spafford MM, Schultz AS, Iley MD, Zawada V.

*PhD †OD, PhD, FAAO ‡PhD, RN §BSc, OD ¶BSc, BEd, MEd Propel Centre for Population Health Impact, Faculty Applied Health Sciences, University of Waterloo, Waterloo, Ontario, Canada (RDK), Center for Global Tobacco Control, Department of Society, Human Development & Health, Harvard School of Public Health, Boston, Massachusetts (RDK), School of Optometry, University of Waterloo, Waterloo, Ontario, Canada (MMS, MDI, VZ), and Cancer Prevention, Cancer Nursing Research, Faculty of Nursing, University of Manitoba, Winnepeg, Manitoba (ASHS).

PURPOSE.: The current pilot study sought to understand optometrists' attitudes toward addressing tobacco use within the scope of their practice, and to identify opportunities within Canada to integrate optometrists as health care partners into the national tobacco cessation network.

METHODS.: A descriptive qualitative design was used to conduct this pilot study. Five focus groups were conducted with 29 informants, including 11 practicing community optometrists and 18 senior Doctor of Optometry students from the University of Waterloo. Rationales, barriers, and opportunities to practice patterns were identified.

RESULTS.: Optometrists and optometry students knew the association of smoking with eye diseases such as age-related macular degeneration and cataract; however, some informants selectively asked patients about smoking behavior based on patient age or visit type. Most informants indicated that they did inform their patients who smoke of their increased risk of developing certain eye diseases; however, very few informants assessed whether their patients wanted to stop smoking and no informants reported that they had ever provided a patient with explicit support for tobacco cessation. This limited role in smoking cessation support for patients due, in part, to insufficient: financial incentives, training and educational tools and materials, knowledge of community resources for cessation treatments, and time during appointments. Several opportunities were identified to better integrate optometry into tobacco control efforts such as optometrists' access to patients, patients' fear of blindness as a tool to motivate behavior changes, and practitioners' openness to change.

CONCLUSIONS.: Optometrists can be a helpful addition to a smoking cessation healthcare network that already involves more than a dozen health care professions including medicine, nursing, pharmacy, dentistry, and dental hygiene. The findings of this study will be used to develop a national survey of Canadian optometrists' practice patterns regarding tobacco use prevention efforts and cessation supports for their patients.

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Curr Opin Ophthalmol. 2011 Apr 1. [Epub ahead of print]

The economics of telemedicine for vitreoretinal diseases.

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PURPOSE OF REVIEW: A literature review was conducted presenting the current data on the economics of telemedicine in vitreoretinal diseases.

RECENT FINDINGS: There have been an increasing number of studies evaluating the cost-effectiveness of telemedicine for vitreoretinal diseases. The availability of ophthalmologists able to screen for these conditions is limited. Teleophthalmology has been playing a larger role in screening for diabetic retinopathy,

retinopathy of prematurity, and age-related macular degeneration. Many telemedicine programs are currently being investigated and implemented.

SUMMARY: Telemedicine is a cost-effective means for screening diabetic retinopathy and retinopathy of prematurity. It can alleviate some of the burden of this growing public health problem. However, the large initial cost associated with beginning a teleophthalmology retinal screening program is a barrier to implementation. Additional studies are needed in the area of telemedicine for age-related macular degeneration.

PMID: 21460727 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2011 Apr 5. [Epub ahead of print]

The impact of the severity of vision loss on vision-specific functioning in a German outpatient population - an observational study.

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

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BACKGROUND: To validate the German-translated VF-14, a vision-specific scale, and determine the relationship between the severity of vision impairment, ocular conditions, and visual functioning.

METHODS: This was a clinic-based, cross-sectional study with 184 patients with low vision and 90 normal-sighted controls recruited from a German eye hospital. Participants underwent a clinical examination and completed the German VF-14 scale. The validity of the VF-14 scale was assessed using Rasch analysis. The main outcome measure was the visual functioning overall score.

RESULTS: The participants' mean ± SD [standard deviation] age was 59.4 ± 21.8 years ,and there were more female (58.4%) than male participants. The main cause of vision loss was age-related macular degeneration [AMD] (n = 54, 19.7%). Rasch analysis substantiated the German VF-14 to be a valid scale to assess visual functioning in the sample. Visual functioning consistently declined with worsening vision. In adjusted-multivariate analysis models, compared to control participants, those with mild, or moderate/severe vision impairment recorded significantly poorer visual functioning scores ($p < 0.05$). The independent association was clinically significant for those with moderate/severe vision impairment. The main ocular conditions were also found to be independently associated with worse visual functioning, with clinical significance found for AMD, diabetic retinopathy, and other retinal diseases.

CONCLUSIONS: Using a psychometrically valid German-translated VF-14, even mild vision impairment was independently associated with poor visual functioning. These findings reinforce the importance of early preventative and rehabilitative efforts to prevent longitudinal deterioration in vision loss.

PMID: 21465288 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Apr 7. [Epub ahead of print]

Risk of falls, injurious falls, and other injuries resulting from visual impairment among older adults with Age-related Macular Degeneration.

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Purpose: Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment among older adults. This study explored the relationship between AMD, falls risk and other injuries and identified visual risk factors for these adverse events.

Methods: Participants included 76 community-dwelling individuals with a range of severity of AMD (mean age, 77.0±6.9 years). Baseline assessment included binocular visual acuity, contrast sensitivity and merged visual fields. Participants completed monthly falls and injury diaries for one year following the baseline assessment.

Results: Overall, 74% of participants reported having either a fall or a non-fall related injury. Fifty-four percent of participants reported a fall and 30% reported more than one fall; of the 102 falls reported, 63% resulted in an injury. Most occurred outdoors (52%), between late morning and late afternoon (61%) and when navigating on level ground (62%). The most common non-fall related injuries were lacerations (36%) and collisions with an object (35%). Reduced contrast sensitivity and visual acuity were associated with increased falls rate, after controlling for age, gender, cognitive function, cataract severity and self-reported physical function. Reduced contrast sensitivity was the only significant predictor of non-fall related injuries.

Conclusion: Among older adults with AMD, increased visual impairment was significantly associated with an increased incidence of falls and other injuries. Reduced contrast sensitivity was significantly associated with both increased rates of falls and other injuries, while reduced visual acuity was only associated with increased fall rate. These findings have important implications for the assessment of visually impaired older adults.

PMID: 21474773 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Apr 7. [Epub ahead of print]

Performance of Automated Drusen Detection by Polarization-sensitive Optical Coherence Tomography.

Schlanitz F, Baumann B, Spalek T, Schütze C, Ahlers C, Pircher M, Götzinger E, Hitzenberger C, Schmidt-Erfurth U.

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Purpose: To estimate the potential of polarization-sensitive optical coherence tomography (PS-OCT) for quantitative assessment of drusen in patients with early age-related macular degeneration (AMD).

Methods: Fifteen eyes of thirteen patients presenting drusen consistent with AREDS 2 and 3 classification were examined ophthalmoscopically, followed by fundus photography, autofluorescence imaging and three-dimensional scanning using a PS-OCT. For the automated evaluation of drusen location, area and volume, a novel segmentation algorithm was developed based on the polarization scrambling characteristics of the retinal pigment epithelium (RPE) and applied to each complete dataset. Subsequently, the drusen in each individual B-scan were identified by two independent expert graders. Accordance between manual and automated segmentation results was analyzed. Errors in the automated segmentation performance were classified as non-significant, moderate or severe.

Results: A total number of 2355 individual drusen, with a mean of 157 drusen per eye, was analyzed. 91.4 % of drusen seen in the individual B-scans were detected manually by both expert graders. The automated segmentation algorithm identified 96.5% of all drusen without significant error. The mean difference in manual and automated drusen area (mean of 4.65 mm(2)) was 0.150. The number of detected drusen was significantly higher with automated than with manual segmentation. PS-OCT segmentation was generally superior to fundus photography ($p<0.001$). Particularly in non-detected drusen, a large variability in drusen morphology was noted.

Discussion: Automated drusen detection based on PS-OCT technology allows a fast and accurate determination of drusen location, number and total area.

PMID: 21474772 [PubMed - as supplied by publisher]

Epidemiology & pathogenesis

J Biol Chem. 2011 Apr 4. [Epub ahead of print]

Complement system dysregulation and inflammation in the retinal pigment epithelium of a mouse model for Stargardt macular degeneration.

Radu RA, Hu J, Yuan Q, Welch DL, Makshanoff J, Lloyd M, McMullen S, Travis GH, Bok D.

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Abstract

Accumulation of vitamin A-derived lipofuscin fluorophores in the retinal pigment epithelium (RPE) is a pathologic feature of recessive Stargardt macular dystrophy, a blinding disease caused by dysfunction or loss of the ABCA4 transporter in rods and cones. Age-related macular degeneration (AMD), a prevalent blinding disease of the elderly, is strongly associated with mutations in the genes for complement-regulatory proteins (CRPs), causing chronic inflammation of the RPE. Here we explore the possible relationship between lipofuscin accumulation and complement activation in vivo. Using the abca4 / mouse-model for recessive Stargardt, we investigated the role of lipofuscin fluorophores (A2E-lipofuscin) on oxidative stress and complement activation. We observed higher expression of oxidative-stress genes and elevated products of lipid peroxidation in eyes from abca4 / versus wild-type mice. We also observed higher levels of complement-activation products in abca4 / RPE cells. Unexpectedly, expression of multiple CRPs, which protect cells from attack by the complement system, were lower in abca4 / versus wild-type RPE. To test whether acute exposure of healthy RPE cells to A2E-lipofuscin affects oxidative stress and expression of CRPs, we fed cultured fetal-derived human RPE (hRPE) cells with rod outer-segments (ROS) from wild-type or abca4 / retinas. In contrast to RPE cells in abca4 / mice, hRPE cells exposed to abca4 / ROS adaptively increased expression of both oxidative-stress and CRP genes. These results suggest that A2E accumulation causes oxidative stress, complement activation and down-regulation of protective CRPs in the Stargardt mouse model. Thus, Stargardt disease and AMD may both be caused by chronic inflammation of the RPE.

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Age-related macular degeneration and the other double helix: The Cogan Lecture.

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Abstract

The study and therapy of age-related macular degeneration (AMD), a leading cause of blindness worldwide, have taken great strides over the past decade. During the same time, a central role for RNA in many human diseases has been discovered. We have identified anti-angiogenic functions for synthetic double stranded RNAs (dsRNAs) in neovascular AMD and cytotoxic functions for endogenous dsRNAs in atrophic AMD. These findings provide new insights into the pathogenesis and therapy of both forms of AMD.

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Genetics

Invest Ophthalmol Vis Sci. 2011 Apr 5. [Epub ahead of print]

A homozygous frameshift mutation in BEST1 causes the classical form of Best disease in an autosomal recessive mode.

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Purpose: Best disease is a monogenic macular degeneration caused mainly by heterozygous mutations in the BEST1 gene. The objective was to characterize the molecular and clinical features of patients with the classical form of Best disease that is inherited in an autosomal recessive mode.

Methods: Clinical evaluation included detailed family history, a full ophthalmologic exam, electrooculography (EOG), electroretinography (ERG), color vision testing, and ocular imaging. Mutation analysis was performed by direct sequencing of PCR products.

Results: We recruited two young siblings affected by Best disease, confirmed by funduscopy, retinal imaging, and electrophysiologic assessment. Molecular analysis revealed a novel homozygous deletion (c.1415delT) in the BEST1 gene leading to a frameshift followed by a premature stop codon, which cosegregated with the disease in a recessive mode. The heterozygous parents had normal visual acuity, normal retinal appearance and function. The two heterozygous grandmothers, ages 61 and 62, also had normal Arden ratios on EOG, but one of them manifested moderate-to-severe dry age-related macular degeneration.

Conclusions: We show here that the typical vitelliform phenotype of Best disease, usually transmitted in an autosomal dominant fashion, can be inherited as an autosomal recessive disease due to homozygosity for a frameshift mutation.

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Mol Med Report. 2010 May-Jun;3(3):469-71. doi: 10.3892/mmr_00000282.

Common polymorphisms of the CFH, LOC 387715/ARMS2 and HTRA1 genes may not influence the intra-familial variability of X-linked juvenile retinoschisis.

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Abstract

X-linked juvenile retinoschisis (XLRS) is the leading cause of juvenile macular degeneration in males and is rare in females. Previous studies have shown that there is a marked intra- and inter-familial variation in disease severity and progression. This suggests that additional factors, such as genetic modifiers and environmental elements, influence disease severity. In order to understand the contribution of genetic modifiers, we aimed to ascertain whether common variants of the CFH, LOC 387715/ARMS2 and HTRA1 genes, which are major risk factors in age-related macular degeneration, contribute to the phenotypic variability of the XLRS disorder. Two unrelated XLRS families were selected, one harboring the missense mutation and the second a nonsense mutation in the RS gene. Both families exhibited variations in clinical phenotype. Genomic DNA from family members were analyzed for the above three genes using the polymerase chain reaction-based restriction fragment length polymorphism method. Our analyses revealed that both families were wild-type with respect to the LOC 387715/ARMS2 and HTRA1 genes. In one family (but not the other), the most severely affected and unaffected individuals were heterozygous for the CFH polymorphisms, while the less severely affected individual was wild-type. However, this alteration did not

necessarily influence disease severity. Although we cannot completely rule out the role of the above genes in determining the phenotypic variability of the disorder, and though the statistical significance of the results could not be assessed due to the small scale of the study, it is unlikely that common polymorphisms of the CFH, LOC 387715/ARMS2 and HTRA1 genes serve as disease modifiers of the XLRS disorder.

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Pre-clinical

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Complement Deposition and Microglial Activation in the Outer Retina in Light-Induced Retinopathy: Inhibition by a 5-HT1A agonist.

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Abstract

Purpose: Increasing evidence supports a role for complement in the pathogenesis of age-related macular degeneration (AMD). This study evaluated retinal microglia, T-lymphocytes, and complement deposition, in a light-induced retinopathy model. The effect of a serotonin (5-hydroxytryptamine, 5-HT(1A)) agonist on these processes was investigated.

Methods: Rats were dark adapted for 24 hrs prior to a 6-hr blue-light exposure. Some animals were pre-dosed (SQ) with AL-8309A. Retinas were evaluated at different times after light exposure. Paraffin sections were antibody stained for a microglial marker (Iba1), a T-lymphocyte marker (CD3), and complement components C1q, C3, Factor B, Factor H and membrane attack complex (MAC).

Results: Light exposure resulted in substantial photoreceptor and RPE loss. Robust microglia activation and migration to the outer retina occurred rapidly. Substantial T-lymphocyte recruitment did not occur. Complement alternative pathway was strongly activated, resulting in deposition of C3, Factor B, Factor H and MAC in the area of photic lesions. Dosing with AL-8309A prevented retinal lesions and decreased microglia activation/recruitment and complement deposition in the outer retina.

Conclusion: In blue-light exposed retinas, microglia were activated and migrated toward the outer retina, while a T-lymphocyte response was minimal. The innate immune system was markedly activated, with substantial complement deposition in the outer retina after light exposure. This complement deposition was prevented by AL-8309A. This model may be useful in the evaluation of complement inhibitors as well as other neuroprotectants intended for ocular use. AL-8309 is under evaluation in the clinic and may be useful in the treatment of AMD.

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