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MD Research News

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Drug treatment

Eye (Lond). 2015 Jun 5. [Epub ahead of print]

Long-term visual outcomes of intravitreal ranibizumab treatment for wet age-related macular degeneration and effect on blindness rates in south-east Scotland.

Borooah S, Jeganathan VS, Ambrecht AM, Oladiwura D, Gavin M, Dhillon B, Cackett P.

Aims: To evaluate patient visual acuity outcomes and blindness rates attributable to wet AMD with a potential 5-year follow-up from intravitreal ranibizumab treatment (IVTR) in south-east Scotland.

Methods: Data was analysed from 104 eyes of 96 patients who initiated treatment prior to September 2008. The main outcome measures were LogMAR visual acuity, number of clinic visits and the number of injections. Annual blind registration data in south-east Scotland were analysed using blind certifications recorded by the Royal National Institute of Blind People.

Results: Patients had a mean clinical follow-up of 4 years and 1 month and a mean loss of 5.5 letters over the study period. Of the treated eyes 9.6% gained ≥15 letters whilst 24.0% lost ≥15 letters during this period. An average of 9.56 injections were administered per patient. The age-sex standardised incidence of legal blindness attributable to wet AMD in south-east Scotland peaked at 9.1 cases per 100 000 of the population in 2006 in either eye. Following the introduction of IVTR there were annual decreases in the incidence of blindness attributable to AMD falling to a trough of 4.8 cases per 100 000 of the population in 2011.

Conclusions: This study demonstrates that the majority of patients in a south-east Scotland maintain their vision following IVTR in wet AMD in the real-world setting. Our study also suggests that the introduction of IVTR has had population wide benefits in reducing the blindness attributable to wet AMD in the south-east Scotland population.Eye advance online publication, 5 June 2015; doi:10.1038/eye.2015.83.

PMID: 26043706 [PubMed - as supplied by publisher]

Int Ophthalmol. 2015 Jun 5. [Epub ahead of print]

Effect of aflibercept in patients with age-related macular degeneration.

Okuma H, Mimura T, Goto M, Kamei Y, Yoshida M, Kondo A, Matsubara M.

Abstract: The purpose of this study was to evaluate the efficacy of standard induction therapy with intravitreal aflibercept (IVA) in patients with exudative age-related macular degeneration (AMD) at 6 months after completion of induction therapy. Eleven eyes with typical AMD (tAMD) and 13 eyes with polypoidal choroidal vasculopathy (PCV) received three monthly doses of IVA (2 mg/0.05 ml in weeks 0, 4, and 8) for

treatment of exudative AMD. Best-corrected visual acuity (BCVA) was measured, and optical coherence tomography was performed at baseline and at each monthly visit until 6 months after IVA. Treatment failure was defined as persistent or recurrent AMD that presented with cystoid macular edema, serous retinal detachment, and pigment epithelium detachment. Mean logMAR BCVA was improved from 0.62 ± 0.46 at baseline to 0.54 ± 0.43 at 6 months after IVA ($p < 0.05$). The success rate was 95.8 % at 3 months and 75.0 % at 6 months after IVA. Failure of IVA was positively associated with the absence of PVD before treatment ($r = 0.35$) and with the AMD type (tAMD, $r = 0.43$) by univariate analysis. Cox proportional hazards analysis demonstrated that the absence of PVD before treatment was associated with an increased risk of failure of IVA (OR = 33.17, $p = 0.0219$). Three months of induction IVA achieved a high success rate in patients with AMD monitored for up to 6 months. Factors associated with failure of IVA were the absence of PVD and the presence of tAMD. Accordingly, continuation of IVA following induction therapy may be beneficial to manage AMD in patients with tAMD or those without PVD.

PMID: 26043678 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2015 Jun;50(3):209-16.

Efficacy/safety of ranibizumab monotherapy or with laser versus laser monotherpay in DME.

Berger A, Sheidow T, Cruess AF, Arbour JD, Courseau AS, de Takacsy F.

OBJECTIVE: To compare the efficacy and safety of ranibizumab 0.5 mg intravitreal injection, as monotherapy or in combination with laser, with laser monotherapy in patients with visual impairment caused by diabetic macular edema.

DESIGN: Twelve-month, multicentre, open-label, parallel-group, randomized, active-control study.

PARTICIPANTS: A total of 220 (ranibizumab monotherapy: n = 75, ranibizumab + laser: n = 73, laser monotherapy: n = 72) patients with a diagnosis of type I or II diabetes and visual impairment caused by macular edema were included in the efficacy analysis.

METHODS: Ranibizumab was initiated with a fixed loading phase of 3 monthly injections followed by as needed therapy until stable vision achievement. Efficacy end points were the change in best corrected visual acuity (BCVA), change in central retinal thickness (CRT) measured by optical coherence tomography, proportion achieving a 15-letter BCVA gain, and 12-month Visual Function Questionnaire-25 (VFQ-25) score. Safety was assessed with the incidence and severity of adverse events.

RESULTS: At 12 months, significant ($p < 0.001$) mean BCVA improvements were observed for both the ranibizumab monotherapy (+8.9 [95% confidence interval (CI) 7.0-10.7] letters) and the ranibizumab + laser (+8.2 [95% CI 6.0-10.4] letters) groups compared with the laser monotherapy group (+0.3 [95% CI -2.9 to 3.5] letters). Similarly, a better response in terms of CRT improvement, BCVA letter gain, and VFQ-25 was observed in both ranibizumab groups compared with laser monotherapy. The safety profile was comparable in the 2 ranibizumab groups.

CONCLUSIONS: Ranibizumab as monotherapy or combined with laser resulted in significantly higher improvements in visual acuity and vision-related quality of life at month 12 as compared with laser monotherapy.

PMID: 26040221 [PubMed - in process]

PLoS One. 2015 Jun 3;10(6):e0128403. eCollection 2015.

Treatment Satisfaction and Well-Being in Patients with Myopic Choroidal Neovascularization Treated with Ranibizumab in the REPAIR Study.

Amoaku WM, Gale RP, Lotery AJ, Menon G, Sivaprasad S, Petrillo J, Quinn J.

Abstract: The Ranibizumab for the Treatment of Choroidal Neovascularisation (CNV) Secondary to Pathological Myopia (PM): an Individualized Regimen (REPAIR) trial was a prospective study exploring the efficacy and safety of intravitreal ranibizumab 0.5 mg using an individualized treatment regimen over 12 months. The current study investigated the impact of treatment with ranibizumab as needed (pro re nata [PRN]) on individuals with myopic choroidal neovascularization (mCNV) in the REPAIR study, using patient-reported outcome measures (PROMs) for treatment satisfaction and well-being. This study included 65 adults with mCNV and a best-corrected visual acuity (BCVA) letter score of 24-78 in the study eye. Patients completed the Macular Disease Treatment Satisfaction Questionnaire (MacTSQ) at months 1, 6 and 12, and the 12-item Well-Being Questionnaire (W-BQ12) at baseline and months 1, 6 and 12. Subgroup analyses investigated the relationship between PROM scores and treatment in the better- or worse-seeing eye (BSE/WSE), number of injections received, baseline BCVA, BCVA improvement and age. Pearson correlations between change in BCVA, MacTSQ scores and W-BQ12 scores were calculated. The main outcome measures were treatment satisfaction measured with the MacTSQ (score 0-72) and well-being measured with the W-BQ12 (score 0-36). Treatment satisfaction significantly increased over the study period ($p = 0.0001$). Mean MacTSQ scores increased by 9.7 and 10.0 in patients treated in their WSE and BSE, respectively. Treatment satisfaction was highest in individuals receiving only one injection at month 1; however, by month 12, scores were similar across injection subgroups. Patients aged 68 years or older had the highest MacTSQ scores. Well-being scores also significantly increased over the study period ($p = 0.03$). Mean W-BQ12 scores increased by 1.7 in patients treated in their WSE and by 2.1 in patients treated in their BSE. Individuals aged 40 years or younger had the greatest increases in general well-being. Patients who experienced stable or improved BCVA at month 12 had greater increases in W-BQ12 scores than those who experienced a decrease. Correlations between BCVA, MacTSQ scores and W-BQ12 scores were largely non-significant. In conclusion, treatment satisfaction and well-being increased during treatment with ranibizumab PRN. Although directly comparable data are limited for the MacTSQ and W-BQ12 in mCNV, these results complement PROM outcomes reported in related studies.

PMID: 26039355 [PubMed - in process]

Ophthalmology. 2015 May 27. [Epub ahead of print]

Intraocular Pressure in Patients with Neovascular Age-Related Macular Degeneration Receiving Intravitreal Aflibercept or Ranibizumab.

Freund KB, Hoang QV, Saroj N, Thompson D.

PURPOSE: To assess change in intraocular pressure (IOP) in patients with neovascular age-related macular degeneration (NVAMD) receiving intravitreal aflibercept injection (IAI) or ranibizumab in VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) 1 and 2 studies.

DESIGN: Analyses from 2 randomized, active-controlled, phase III trials.

PARTICIPANTS: A total of 2457 patients with NVAMD.

METHODS: Patients received IAI 2 mg every (q) 4 weeks (2q4), 0.5 mg q4 weeks (0.5q4), 2 mg q8 weeks (after 3 monthly doses; 2q8), or ranibizumab 0.5 mg q4 weeks (Rq4) for 52 weeks. At week 52, patients were switched to a variable regimen requiring at least quarterly dosing and allowing interim injections based on anatomic and visual assessment.

MAIN OUTCOME MEASURES: Pre-injection IOP was analyzed in study and uninjected fellow eyes from baseline to week 96. Prespecified end points included mean change in IOP from baseline and prevalence of a >21 mmHg and >10 mmHg increase in IOP from baseline. Cumulative incidence of sustained (at 2 consecutive visits) IOP >21 mmHg, a single event of IOP >25 mmHg, and sustained IOP increase from baseline (≥5 mmHg) was also evaluated.

RESULTS: Mean IOP change from baseline over 96 weeks in all IAI groups was consistently lower than in the Rq4 group, and this finding was replicated in both trials. In an analysis integrating both studies, the

proportion of study eyes with IOP >21 mmHg at week 96 was 20.2%, 14.2%, 12.1%, and 12.5% in Rq4, 2q4, 2q8, and 0.5q4, respectively. Reduction in risk, relative to Rq4, of having sustained IOP >21 mmHg over 96 weeks was 62% (95% confidence interval [CI], 36%-78%), 50% (95% CI, 19%-70%), and 69% (95% CI, 45%-84%) for 2q4, 2q8, and 0.5q4, respectively. Risk reduction in the IAI groups for a sustained IOP increase ≥5 mmHg was 31% (95% CI, 8%-48%), 38% (95% CI, 17%-54%), and 47% (95% CI, 27%-61%), respectively. In uninjected fellow eyes, only sustained IOP >21 mmHg events were higher in the Rq4 group compared with all IAI groups.

CONCLUSIONS: Incidence of elevated IOP in eyes with NVAMD was lower in all IAI groups than in the ranibizumab group.

PMID: 26025097 [PubMed - as supplied by publisher]

Korean J Ophthalmol. 2015 Jun;29(3):190-4. Epub 2015 May 20.

Assessment of Patient Pain Experience during Intravitreal 27-Gauge Bevacizumab and 30-Gauge Ranibizumab Injection.

Güler M, Bilgin B, Çapkın M, Şimşek A, Bilak Ş.

PURPOSE: To compare pain scores of patients during intravitreal 27-gauge bevacizumab and 30-gauge ranibizumab injection procedures.

METHODS: Seventy eyes of 70 patients who had not previously undergone intravitreal anti-vascular endothelial growth factor therapy were included in this study. Thirty-five patients received ranibizumab and 35 patients received bevacizumab. The diagnoses of the patients were: 27 age related macular degeneration, 15 diabetic macular edema, 9 diabetic vitreous hemorrhage, 6 central retinal vein occlusion, 11 branch retinal vein occlusion and 2 central serous chorioretinopathy. Bevacizumab (1.25 mg/0.05 mL) was injected into the vitreous cavity using a 27-gauge needle, and ranibizumab (0.5 mg/0.05 mL) was injected with 30-gauge needle. Patients were asked just after the injection to rate their perceived pain during the injection using the visual analogue scale (VAS) of 0 (no pain) to 10 (unbearable/worst pain). The average of these scores was used as the primary outcome.

RESULTS: The VAS pain scores in the ranibizumab and bevacizumab groups were 1.06 ± 0.91 (range, 0 to 3) and 1.94 ± 1.55 (range, 0 to 7), respectively, a significant difference ($p = 0.005$). Patients <65 and ≥65 years of age in both the ranibizumab and bevacizumab groups were then compared. For patients <65, there was a significant difference in the average VAS pain scores between groups ($p = 0.003$). However, for patients ≥65 years, there was not a significant difference in the average VAS pain scores between groups ($p = 0.238$). Female and male patients in both ranibizumab and bevacizumab groups were also compared. For female patients, there was a significant difference in the average VAS pain scores between groups ($p = 0.016$), although not for male patients ($p = 0.078$).

CONCLUSIONS: Thirty-gauge intravitreal injection is more comfortable than 27-gauge injection. Injection of bevacizumab with 30-gauge needle syringes may be more tolerable for patients.

PMID: 26028948 [PubMed - in process] PMCID: PMC4446560

Ophthalmology. 2015 May 30. [Epub ahead of print]

Vitreomacular Interface after Anti-Vascular Endothelial Growth Factor Injections in Neovascular Age -Related Macular Degeneration.

Veloso CE, Kanadani TM, Pereira FB, Nehemy MB.

PURPOSE: To evaluate the incidence of posterior vitreous detachment (PVD) induced by intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents in cases of neovascular age-related macular degeneration (AMD).

DESIGN: Cohort study conducted at a single tertiary referral vitreoretinal practice.

PARTICIPANTS: A total of 396 eyes of 295 patients were diagnosed with neovascular AMD between 2009 and 2014. A total of 125 eyes of 112 patients met the inclusion criteria and were evaluated in this study.

METHODS: This study included patients with neovascular AMD who presented vitreomacular adhesion (VMA) detected by spectral-domain optical coherence tomography (OCT) at baseline. Eyes with VMA were classified according to the diameter of vitreous attachment to the macular surface measured by OCT, with attachment of ≤1500 μm defined as focal and attachment of >1500 μm defined as broad. All patients received at least 3 monthly intravitreal injections of anti-VEGF agents. Follow-up visits were performed 1 month after each intravitreal injection and included OCT analysis to evaluate the incidence of PVD.

MAIN OUTCOME MEASURES: Posterior vitreous detachment induced by anti-VEGF injections.

RESULTS: The mean follow-up period was 21.3 months (range, 3-59 months). The mean number of intravitreal injections was 8.3 (range, 3-29 injections). Intravitreal drugs used in the study were ranibizumab (51.5%), bevacizumab (33.5%), and aflibercept (15.0%). Seven eyes (5.6%) developed PVD after intravitreal drug injection (3 eyes after the first intravitreal injection: bevacizumab in 1 and ranibizumab in 2; 2 eyes after the second injection: ranibizumab in 1 and bevacizumab in 1; 1 eye after the fourth injection: ranibizumab; and 1 eye after the sixth injection: aflibercept). A total of 118 eyes remained with persistent VMA. All 7 eyes that developed PVD were classified as having focal VMA, with the diameter of vitreous attachment ranging from 210 to 1146 μm (mean, 600 μm).

CONCLUSIONS: Intravitreal injections of commonly used anti-VEGF intravitreal drugs rarely induce PVD in patients with neovascular AMD. Eyes with focal VMA have a greater chance to develop PVD than eyes with a broad area of VMA.

PMID: 26038338 [PubMed - as supplied by publisher]

Ophthalmology. 2015 May 28. [Epub ahead of print]

VEGFR2 Gene Polymorphisms and Response to Anti-Vascular Endothelial Growth Factor Therapy in Age-Related Macular Degeneration.

Hagstrom SA, Ying GS, Maguire MG, Martin DF; CATT Research Group, Gibson J, Lotery A, Chakravarthy U; IVAN Study Investigators.

PURPOSE: A previously published study demonstrated a pharmacogenetic association between the minor alleles of 2 VEGFR2 single nucleotide polymorphisms (SNPs) and greater improvement in visual acuity (VA) to treatment with ranibizumab, an anti-vascular endothelial growth factor (VEGF) drug, in patients with neovascular age-related macular degeneration (AMD). We evaluated whether this association was replicated among patients who participated in the Comparison of AMD Treatments Trials (CATT) or the Alternative Treatments to Inhibit VEGF in Patients with Age-Related Choroidal Neovascularisation (IVAN) trial.

DESIGN: Cohort studies within randomized clinical trials.

PARTICIPANTS: Eight hundred thirty-five patients participating in CATT and 512 patients participating in IVAN.

METHODS: Each patient was genotyped for the SNPs rs4576072 and rs6828477 in the VEGFR2 gene.

MAIN OUTCOMES MEASURES: Mean change in VA from baseline to 1 year after initiation of treatment with ranibizumab or bevacizumab. Differences in VA response between the patient group homozygous for the minor allele of each SNP and the other genotype groups were evaluated with analysis of variance. Differences in VA response by the number of minor alleles present for either SNP or both combined were evaluated with tests of linear trend. Analyses were conducted separately for CATT and IVAN participants

and with both the studies combined.

RESULTS: No statistically significant difference in mean change in VA was identified between genotypes of either SNP (P ≥ 0.05). Furthermore, a stepwise analysis failed to show a significant interaction for either SNP based on the number of minor alleles present. The lack of association was similar in both the CATT and IVAN cohorts and whether the analysis combined patients treated with either ranibizumab or bevacizumab or when restricted to patients treated with ranibizumab only.

CONCLUSIONS: The CATT and IVAN data do not support a pharmacogenetic association between the 2 VEGFR2 SNPs, rs4576072 and rs6828477, and change in VA in response to anti-VEGF therapy in patients with neovascular AMD.

PMID: 26028346 [PubMed - as supplied by publisher]

Retina. 2015 May 29. [Epub ahead of print]

RANIBIZUMAB PLUS PROMPT OR DEFERRED LASER FOR DIABETIC MACULAR EDEMA IN EYES WITH VITRECTOMY BEFORE ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY.

Bressler SB, Melia M, Glassman AR, Almukhtar T, Jampol LM, Shami M, Berger BB, Bressler NM; Diabetic Retinopathy Clinical Research Network.

BACKGROUND: The approach to managing diabetic macular edema in eyes with previous vitrectomy is based on limited evidence. Therefore, an exploratory post hoc assessment of 3-year data from eyes with and without vitrectomy before randomization in a DRCR.net trial that evaluated ranibizumab + prompt or deferred laser for diabetic macular edema is presented.

METHODS: Visual acuity and optical coherence tomography outcomes were compared between eyes with and without previous vitrectomy.

RESULTS: At baseline, eyes with previous vitrectomy (n = 25) had longer duration of diabetes, worse visual acuity, less thickened central subfield measurements on optical coherence tomography and were more apt to have worse diabetic retinopathy severity level or previous treatment for macular edema or cataract surgery than eyes without a history of vitrectomy (n = 335). Analyses adjusted for these baseline imbalances did not identify substantial differences between eyes with and without previous vitrectomy at each annual visit through 3 years for the favorable visual acuity, optical coherence tomography central subfield thickness, or volume outcomes, although optical coherence tomography improvement appeared slower in vitrectomy eyes during the first year.

CONCLUSION: This study provides little evidence that the beneficial clinical outcomes for patients with center-involved diabetic macular edema treated with anti-vascular endothelial growth factor are affected in the long term by previous vitrectomy.

PMID: 26035510 [PubMed - as supplied by publisher]

BMJ Open. 2015 Jun 5;5(6):e007527.

Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: a network meta-analysis.

Regnier SA, Larsen M, Bezlyak V, Allen F.

OBJECTIVE: To compare the efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion (BRVO).

DESIGN: Randomised controlled trials (RCTs) evaluating the efficacy and safety of approved treatments for

macular oedema secondary to BRVO were identified from an updated systematic review.

SETTING: A Bayesian network meta-analysis of RCTs of treatments for macular oedema secondary to BRVO.

INTERVENTIONS: Ranibizumab 0.5 mg pro re nata, aflibercept 2 mg monthly (2q4), dexamethasone 0.7 mg implant, laser photocoagulation, ranibizumab+laser, or sham intervention. Bevacizumab and triamcinolone were excluded.

OUTCOME MEASURES: Efficacy outcomes were mean change in best corrected visual acuity (Early Treatment Diabetic Retinopathy Study scale) and the percentage of patients gaining ≥15 letters. Safety outcome was the percentage of patients with increased intraocular pressure (IOP)/ocular hypertension (OH).

RESULTS: 8 RCTs were identified for inclusion with 1743 adult patients. The probability of being the most efficacious treatment at month 6 or 12 based on letters gained was 54% for ranibizumab monotherapy, 30% for aflibercept, 16% for ranibizumab plus laser (adjunctive or prompt), and 0% for dexamethasone implant, laser or sham. The probability of being the most efficacious treatment for patients gaining ≥15 letters was 39% for aflibercept, 35% for ranibizumab monotherapy, 24% for ranibizumab plus laser, 2% for dexamethasone implant, and less than 1% for laser or sham. There was no statistical difference between ranibizumab monotherapy and aflibercept for letters gained (+1.4 letters for ranibizumab vs aflibercept with 95% credible interval (CrI) of -5.2 to +8.5 letters) or the OR for gaining ≥15 letters: 1.06 (95% CrI 0.16 to 8.94)). Dexamethasone implant was associated with significantly higher IOP/OH than antivascular endothelial growth factor agents (OR 13.1 (95% CrI 1.7 to 116.9)).

CONCLUSIONS: There was no statistically significant difference between ranibizumab and aflibercept.

PMID: 26048209 [PubMed - in process]

Retina. 2015 May 27. [Epub ahead of print]

INCIDENCE OF SUSTAINED OCULAR HYPERTENSION USING PREPACKAGED VERSUS FRESHLY PREPARED INTRAVITREAL BEVACIZUMAB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Storey PP, Ho V, Yeh S, Reddy S, Fang-Yen NH, Pequignot E, Leiby BE, Fineman M, Garg S, Hubbard GB 3rd, Hsu J.

PURPOSE: To compare the incidence of sustained ocular hypertension (OHT) after intravitreal injections of prepackaged versus freshly prepared bevacizumab monotherapy for the treatment of neovascular age-related macular degeneration.

METHODS: Charts of 1,216 patients with neovascular age-related macular degeneration receiving intravitreal bevacizumab monotherapy at 2 retina practices using different preparations of bevacizumab between January 1, 2009, and December 31, 2011, were reviewed. Primary outcome was incidence of sustained OHT, defined as intraocular pressure >25 mmHg with an increase ≥6 from baseline on ≥2 consecutive visits or requiring treatment.

RESULTS: A total of 6,479 injections in 740 eyes of 634 patients were included and 14 eyes (0.81% incidence per eye-year) developed sustained OHT. For eyes receiving prepackaged bevacizumab, 10 of 339 eyes (1.39% incidence per eye-year) developed sustained OHT compared with 4 of 401 eyes (0.39% incidence per eye-year) receiving freshly prepared bevacizumab, giving an incidence rate ratio of 3.55 (95% confidence interval, 0.93-13.49; P = 0.063). All eyes that developed sustained OHT achieved intraocular pressure control with observation or topical therapy alone.

CONCLUSION: Incidence of sustained OHT after intravitreal bevacizumab is low. We found a trend toward

higher rates of sustained OHT with prepackaged bevacizumab although this difference was not statistically or clinically significant.

PMID: 26035396 [PubMed - as supplied by publisher]

Singapore Med J. 2015 May;56(5):237-247.

Advances in the management of diabetic macular oedema based on evidence from the Diabetic Retinopathy Clinical Research Network.

Lim LT, Chia SN, Ah-Kee EY, Chew N, Gupta M.

Abstract: The Diabetic Retinopathy Clinical Research Network (DRCR.net) performs studies on new treatments for diabetic retinopathy. This review aims to summarise recent findings from DRCR.net studies on the treatment of diabetic macular oedema. We performed a PubMed search of articles from the DRCR.net, which included all studies pertaining to the treatment of diabetic maculopathy. The main outcome measures were retinal thickening as assessed by central subfield thickness on optical coherence tomography and improvement of visual acuity on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Findings from each study were divided into modalities of treatment, namely photocoagulation, bevacizumab, triamcinolone, ranibizumab and vitrectomy. While modified ETDRS focal/grid laser remains the standard of care, intravitreal corticosteroids or anti-vascular endothelial growth factor agents have also proven to be effective, although they come with associated side effects. The choice of treatment modality for diabetic macular oedema is a clinical judgement call, and depends on the patient's clinical history and assessment.

PMID: 26034315 [PubMed - as supplied by publisher] PMCID: PMC4447924

Indian J Ophthalmol. 2015 Apr;63(4):362-3.

Full thickness macular hole following intravitreal ranibizumab injection for diabetic macular edema; a rare complication or coincidence?

Arifoglu HB, Karatepe Hashas AS1, Ersekerci TL, Atas M.

PMID: 26044487 [PubMed - in process]

Ann Acad Med Singapore. 2015 Apr;44(4):116-8.

A Decade of Progress in the Understanding, Prevention and Treatment of Age-related Macular Degeneration in Singapore.

Wagle AM.

PMID: 26041634 [PubMed - in process]

Other treatment & diagnosis

Eye (Lond). 2015 Jun 5. [Epub ahead of print]

Retinal pigment epithelium transplantation: concepts, challenges, and future prospects.

Alexander P, Thomson HA, Luff AJ, Lotery AJ.

Abstract: The retinal pigment epithelium (RPE) is a single layer of cells that supports the light-sensitive

photoreceptor cells that are essential for retinal function. Age-related macular degeneration (AMD) is a leading cause of visual impairment, and the primary pathogenic mechanism is thought to arise in the RPE layer. RPE cell structure and function are well understood, the cells are readily sustainable in laboratory culture and, unlike other cell types within the retina, RPE cells do not require synaptic connections to perform their role. These factors, together with the relative ease of outer retinal imaging, make RPE cells an attractive target for cell transplantation compared with other cell types in the retina or central nervous system. Seminal experiments in rats with an inherited RPE dystrophy have demonstrated that RPE transplantation can prevent photoreceptor loss and maintain visual function. This review provides an update on the progress made so far on RPE transplantation in human eyes, outlines potential sources of donor cells, and describes the technical and surgical challenges faced by the transplanting surgeon. Recent advances in the understanding of pluripotent stem cells, combined with novel surgical instrumentation, hold considerable promise, and support the concept of RPE transplantation as a regenerative strategy in AMD.Eye advance online publication, 5 June 2015; doi:10.1038/eye.2015.89.

PMID: 26043704 [PubMed - as supplied by publisher]

Retina. 2015 May 27. [Epub ahead of print]

RETINAL ANGIOMATOUS PROLIFERATION: A Quantitative Analysis of the Fundoscopic Features of the Fellow Eye.

Marques JP, Laíns I, Costa MÂ, Pires I, da Luz Cachulo M, Figueira J, Silva R.

PURPOSE: To quantitatively analyze and compare the fundoscopic features between fellow eyes of retinal angiomatous proliferation and typical exudative age-related macular degeneration and to identify possible predictors of neovascularization.

METHODS: Retrospective case-control study. Seventy-nine fellow eyes of unilateral retinal angiomatous proliferation (n = 40) and typical exudative age-related macular degeneration (n = 39) were included. Fundoscopic features of the fellow eyes were assessed using digital color fundus photographs taken at the time of diagnosis of neovascularization in the first affected eye. Grading was performed by two independent graders using RetmarkerAMD, a computer-assisted grading software based on the International Classification and Grading System for age-related macular degeneration.

RESULTS: Baseline total number and area (square micrometers) of drusen in the central 1,000, 3,000, and 6,000 μm were considerably inferior in the fellow eyes of retinal angiomatous proliferation, with statistically significant differences ($P < 0.05$) observed in virtually every location (1,000, 3,000, and 6,000 μm). A soft drusen (≥125 μm) area >510,196 μm in the central 6,000 μm was associated with an increased risk of neovascularization (hazard ratio, 4.35; 95% confidence interval [1.56-12.15]; $P = 0.005$).

CONCLUSION: Baseline fundoscopic features of the fellow eye differ significantly between retinal angiomatous proliferation and typical exudative age-related macular degeneration. A large area (>510,196 μm) of soft drusen in the central 6,000 μm confers a significantly higher risk of neovascularization and should be considered as a phenotypic risk factor.

PMID: 26035395 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2015 Jun 1. [Epub ahead of print]

Best-corrected visual acuity and retinal thickness are associated with improved cortical visual processing in treated wet AMD patients.

Vottonen P, Pääkkönen A, Tarkka IM, Kaarniranta K.

PURPOSE: In response to anti-VEGF treatment for wet AMD retinal anatomy and visual acuity is often

remedied. In our previous study, we showed that visual evoked potentials (VEP) improve following successful anti-VEGF treatment. The aim of this study was to investigate, how visual acuity and retinal thickness changes are reflected in VEP parameters. Moreover, we wanted to assess the feasibility of VEP as a novel monitoring tool for wet AMD patients.

METHODS: A total of 16 patients and six control subjects were enrolled in this study. Patients received three bevacizumab intravitreal injections. At the beginning of the study and four to 6 weeks after the last injection, the best-corrected visual acuity (BCVA) test, full biomicroscope examination, OCT analysis and VEP were performed.

RESULTS: In treated eyes, logMAR visual acuity improved on average 0.18 ± 0.32 units, OCT retinal thickness decreased 170 ± 200 micrometres and VEP amplitude increased 1.0 ± 1.4 microvolts. All changes were significant at $p < 0.05$. There was a significant correlation between the relative changes of VEP amplitude and retinal thickness $r = -0.630$ ($p < 0.05$), and between visual acuity (logMAR) and retinal thickness $r = 0.576$ ($p < 0.05$).

CONCLUSION: We showed that both the increase in VEP amplitude and the improvement in visual acuity are associated with the decrease in retinal thickness in treated wet AMD patients. The results do not indicate additional usefulness of VEP in the diagnosis or monitoring of wet AMD.

PMID: 26031317 [PubMed - as supplied by publisher]

Dis Model Mech. 2015 May 1;8(5):421-427.

Cellular models and therapies for age-related macular degeneration.

Forest DL, Johnson LV, Clegg DO.

Abstract: Age-related macular degeneration (AMD) is a complex neurodegenerative visual disorder that causes profound physical and psychosocial effects. Visual impairment in AMD is caused by the loss of retinal pigmented epithelium (RPE) cells and the light-sensitive photoreceptor cells that they support. There is currently no effective treatment for the most common form of this disease (dry AMD). A new approach to treating AMD involves the transplantation of RPE cells derived from either human embryonic or induced pluripotent stem cells. Multiple clinical trials are being initiated using a variety of cell therapies. Although many animal models are available for AMD research, most do not recapitulate all aspects of the disease, hampering progress. However, the use of cultured RPE cells in AMD research is well established and, indeed, some of the more recently described RPE-based models show promise for investigating the molecular mechanisms of AMD and for screening drug candidates. Here, we discuss innovative cell-culture models of AMD and emerging stem-cell-based therapies for the treatment of this vision-robbing disease.

PMID: 26035859 [PubMed - as supplied by publisher] PMCID: PMC4415892

Eye (Lond). 2015 Jun 5. [Epub ahead of print]

Performance of a computerised visual acuity measurement device in subjects with age-related macular degeneration: comparison with gold standard ETDRS chart measurements.

Bokinni Y, Shah N, Maguire O, Laidlaw DA.

Purpose: The aim of the study was to compare the performance of two different COMPlog computerised, single letter scoring, visual acuity (VA) measurements against gold standard Early Treatment Diabetic Retinopathy Study (ETDRS) chart measurements in patients with age-related macular degeneration (AMD). One computerised algorithm presented five and the other presented three letters per line; both computerised algorithms utilised half, rather than the full-letter width spacing standard on ETDRS charts that might induce crowding, fixation problems, increased test-retest variability (TRV), and bias.

Methods: Fifty patients with AMD (mean age 83 years) underwent timed test and retest VA measurements

using ETDRS charts and COMPlog five (C5) and three (C3) letters per line computerised VA measurement algorithms. All tests utilised single-letter scoring methodology. Bland and Altman methods were employed. Performance was measured in terms of bias, TRV, and test time.

Results: The C5 and C3 scores showed no bias compared with the ETDRS chart measurements. C5 measurements had equal TRV to the ETDRS chart (±0.13 logMAR) with similar median test times (105 and 96 s, respectively). C3 measurements were slightly more variable (TRV ±0.17 logMAR), but 30 s quicker than ETDRS chart measurements.

Conclusions: The closer letter spacing employed in COMPlog testing algorithms appears to have no adverse effect on VA measurements compared with the gold standard ETDRS chart in patients with AMD. The three letter per line testing algorithm facilitates faster testing but with a two letter increase in TRV.Eye advance online publication, 5 June 2015; doi:10.1038/eye.2015.94.

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Pathogenesis

Ophthalmologica. 2015 Jun 4. [Epub ahead of print]

Idebenone Prevents Oxidative Stress, Cell Death and Senescence of Retinal Pigment Epithelium Cells by Stabilizing BAX/Bcl-2 Ratio.

Arend N, Wertheimer C, Laubichler P, Wolf A, Kampik A, Kernt M.

PURPOSE: Age-related macular degeneration (AMD) is one of the leading causes of blindness. Degeneration of the retinal pigment epithelium (RPE) is pathognomonic for the disease, and oxidative stress plays an important role in the pathogenesis of this disease. This study investigates potential antiapoptotic and cytoprotective effects of idebenone on cultured RPE cells (ARPE-19) under conditions of oxidative stress.

METHODS: ARPE-19 cells were treated with 1-100 µM idebenone. Cell viability (MTT assay), induction of intracellular reactive oxygen species (ROS) and histone-associated DNA fragments in mono- and oligonucleosomes, expression of proapoptotic BAX and antiapoptotic Bcl-2 as well as senescence-associated β-galactosidase (SA-β-Gal) activity were investigated under exposure to hydrogen peroxide (H2O2).

RESULTS: Idebenone concentrations from 1 to 20 µM showed no toxic effects on ARPE-19 cells. When cells were treated with H2O2, pretreatment with 5, 7.5, 10, and 20 µM idebenone led to a significant increase in the viability of ARPE-19 cells. In addition, idebenone pretreatment significantly attenuated the induction of SA-β-Gal and intracellular ROS as well as the amount of histone-associated DNA fragments after treatment with H2O2. The reduction of proapoptotic BAX and the elevation of antiapoptotic Bcl-2 under idebenone show that this process is rather mediated by inhibiting H2O2-induced apoptosis, not necrosis.

CONCLUSION: In this study, idebenone increased survival of ARPE-19 cells and reduced cell death, senescence, and oxidative stress by stabilizing the BAX/Bcl-2 ratio. © 2015 S. Karger AG, Basel.

PMID: 26044821 [PubMed - as supplied by publisher]

Exp Eye Res. 2015 May 28. [Epub ahead of print]

Iron accumulation in Bruch's membrane and melanosomes of donor eyes with age-related macular degeneration.

Biesemeier A, Yoeruek E, Eibl O, Schraermeyer U.

Abstract: Iron (Fe) accumulation in cytoplasmic storages of the retina and retinal pigment epithelium (RPE) with age has been reported to be a contributing factor to the onset and progression of Age-related Macular Degeneration (AMD). This work investigated whether iron can also be stored in specialized metal-binding melanosomes of the RPE and choroid and in age pigments of the RPE (lipofuscin and melanolipofuscin). As accumulation of debris in Bruch's membrane is an additional hallmark of AMD, the elemental composition of Bruch's membrane was also investigated. Perimacular sections of the retina-choroid complex of six eyes of AMD donors and of seven age-matched healthy controls were investigated using Analytical Electron Microscopy (AEM). The melanosomes of the RPE and choroidal melanocytes of all AMD donors contained about two times higher iron mole fractions (0.06-0.07 at%) compared to the controls, which showed only minor iron mole fractions at or below the detection limit of 0.02 at%. Only melanosomes that contained iron, showed also significant lead peaks (both AMD and control about 0.08 at%). In addition, the electron-dense part of melanolipofuscin granules in the RPE accumulated iron and lead, both for control and AMD donors. Iron in lipofuscin was below the detection limit. The elastic layer of Bruch's membrane of all AMD donors also contained significantly higher iron mole fractions compared to controls (about 0.08 at% Fe), predominantly in areas that were also rich in calcium (Ca) and phosphorus (P), suggesting calcification. Indeed, five of the six AMD donors but only one of the seven controls showed nanocrystalline hydroxyapatite calcifications. Note that such nanocrystalline material can only be detected in EM samples without heavy metal (osmiumtetroxide, uranylacetate) staining. In conclusion, iron accumulation in melanosomal storages and within calcified Bruch's membrane is more pronounced in donors suffering from AMD compared to age-matched controls. This work underlines the common hypothesis that heavy metal homeostasis plays an important role in age-related neuropathy.

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Biochim Biophys Acta. 2015 May 27. [Epub ahead of print]

Alpha crystallins in the retinal pigment epithelium and implications for the pathogenesis and treatment of age-related macular degeneration.

Kannan R, Sreekumar PG, Hinton DR.

BACKGROUND: αA- and αB crystallins are principal members of the small heat shock protein family and elicit both a cell protective function and a chaperone function. α-Crystallins have been found to be prominent proteins in normal and pathological retina emphasizing the importance for in-depth understanding of their function and significance.

SCOPE OF REVIEW: Retinal pigment epithelial cells (RPE) play a vital role in the pathogenesis of age-related macular degeneration (AMD). This review addresses a number of cellular functions mediated by α-crystallins in the retina. Prominent expression of αB crystallin in mitochondria may serve to protect cells from oxidative injury. αB crystallin as secretory protein via exosomes can offer neuroprotection to adjacent RPE cells and photoreceptors. The availability of chaperone-containing minipeptides of αB crystallin could prove to be a valuable new tool for therapeutic treatment of retinal disorders.

MAJOR CONCLUSIONS: α-Crystallins are expressed in cytosol and mitochondria of RPE cells and are regulated during oxygen-induced retinopathy and during development. α-Crystallins protect RPE from oxidative-and ER stress-induced injury and autophagy. αB-Crystallin is a modulator of angiogenesis and vascular endothelial growth factor. αB Crystallin is secreted via exosomal pathway. Minichaperone peptides derived from αB Crystallin prevent oxidant induced cell death and have therapeutic potential.

GENERAL SIGNIFICANCE: Overall, this review summarizes several novel properties of α-crystallins and their relevance to maintaining normal retinal function. In particular, the use of α-crystallin derived peptides is a promising therapeutic strategy to combat retinal diseases such as AMD. This article is part of a Special Issue entitled Crystallin biochemistry in health and disease.

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J Med Chem. 2015 Jun 2. [Epub ahead of print]

Synthesis and Biological Evaluation of Novel Homoisoflavonoids for Retinal Neovascularization.

Basavarajappa HD, Lee B, Lee H, Sulaiman RS, An H, Magaña C, Shadmand M, Vayl A, Rajashekhar G, Kim EY, Suh YG, Lee K, Seo SY, Corson TW.

Abstract: Eye diseases characterized by excessive angiogenesis such as wet age-related macular degeneration, proliferative diabetic retinopathy, and retinopathy of prematurity are major causes of blindness. Cremastranone is an anti-angiogenic, naturally occurring homoisoflavanone with efficacy in retinal and choroidal neovascularization models and antiproliferative selectivity for endothelial cells over other cell types. We undertook a cell-based structure-activity relationship study to develop more potent cremastranone analogs, with improved antiproliferative selectivity for retinal endothelial cells. Phenylalanyl-incorporated homoisoflavonoids showed improved activity and remarkable selectivity for retinal microvascular endothelial cells. A lead compound inhibited angiogenesis in vitro without inducing apoptosis, and had efficacy in the oxygen-induced retinopathy model in vivo.

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Exp Biol Med (Maywood). 2015 Jun 2. [Epub ahead of print]

Retinal pigment epithelial cell proliferation.

Stern J, Temple S.

Abstract: The human retinal pigment epithelium forms early in development and subsequently remains dormant, undergoing minimal proliferation throughout normal life. Retinal pigment epithelium proliferation, however, can be activated in disease states or by removing retinal pigment epithelial cells into culture. We review the conditions that control retinal pigment epithelial proliferation in culture, in animal models and in human disease and interpret retinal pigment epithelium proliferation in context of the recently discovered retinal pigment epithelium stem cell that is responsible for most in vitro retinal pigment epithelial proliferation. Retinal pigment epithelial proliferation-mediated wound repair that occurs in selected macular diseases is contrasted with retinal pigment epithelial proliferation-mediated fibroblastic scar formation that underlies proliferative vitreoretinopathy. We discuss the role of retinal pigment epithelial proliferation in age-related macular degeneration which is reparative in some cases and destructive in others. Macular retinal pigment epithelium wound repair and regression of choroidal neovascularization are more pronounced in younger than older patients. We discuss the possibility that the limited retinal pigment epithelial proliferation and latent wound repair in older age-related macular degeneration patients can be stimulated to promote disease regression in age-related macular degeneration.

PMID: 26041390 [PubMed - as supplied by publisher]

Int Ophthalmol Clin. 2015 Summer;55(3):63-78.

Inflammatory Mechanisms of Age-related Macular Degeneration.

Knickelbein JE, Chan CC, Sen HN, Ferris FL, Nussenblatt RB.

PMID: 26035762 [PubMed - in process]

Genetics

Int J Clin Exp Pathol. 2015 Mar 1;8(3):3186-91. eCollection 2015.

Association of complement factor H gene polymorphisms with age-related macular egeneration susceptibility.

Hao XF, Xie LK, Tang YZ, Xie WK, Zhang ZF, Qi YX, Xiao WZ, Zhang J.

OBJECTIVE: This study was aimed to confirm whether I62V and Y402H polymorphisms of complement factor H (CFH) were risk factors for age-related macular degeneration (AMD).

METHOD: 109 AMD patients and 165 AMD-free controls were enrolled in the study. The I62V and Y402H polymorphisms were analyzed by polymerase chain reaction-restriction fragment length of polymorphism (PCR-RFLP). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by the X(2) test to assess the relationship of I62V and Y402H polymorphisms with AMD risk. Analysis of haplotype and stratification by age and smoking status was conducted as well.

RESULTS: AA genotype and A allele of I62V polymorphism was significantly associated with increased risk for AMD (OR = 3.75, 95% CI = 1.70-8.30; OR = 1.64, 95% CI = 1.14-2.36). For Y402H polymorphism, CT genotype showed strong effects on the occurrence of AMD (OR = 2.10, 95% CI = 1.04-4.27). Moreover, C allele was also a risk factor for AMD (OR = 1.95, 95% CI = 1.02-3.72). The haplotypes analysis suggested that the risk for AT haplotype carriers was high, compared with GT haplotype (OR = 3.91, 95% CI = 2.58-5.94). In addition, we found that smoking status could affect the genotype distribution of Y402H polymorphism ($P < 0.05$).

CONCLUSIONS: Our results revealed that CFH polymorphisms I62V and Y402H might be associated with the susceptibility to AMD in Chinese population.

PMID: 26045838 [PubMed - in process] PMCID: PMC4440147

Exp Gerontol. 2015 Jun 3. [Epub ahead of print]

Leukocyte telomere length is associated with advanced age-related macular degeneration in the Han Chinese population.

Weng X, Zhang H, Kan M, Ye J, Liu F, Wang T, Deng J, Tan Y, He L, Liu Y.

Abstract: Telomeres located at the ends of chromosomes are involved in genomic stability and play a key role in various cancers and age-related diseases. Age-related macular degeneration (AMD) is a late-onset, age-associated progressive neurodegenerative disease, which includes the geographic atrophy (GA) subtype and the choroidal neovascularization (CNV) subtype. To better understand how leukocyte telomere length (LTL) is related to AMD, we conducted an association study in 197 AMD patients and 259 healthy controls using the established quantitative PCR technique. Logistic regression was performed to evaluate the association of LTL and AMD with the age-adjusted ratio of the telomere length to the copy number of a single-copy gene (T/S). Notably, we found a significant association between AMD and LTL (OR =2.24; 95% CI=1.68-3.07; P=0.0001) after adjusting for age and sex. Furthermore, the results showed a strongly significant association between the GA subtype and the LTL (OR =4.81; 95% CI=3.15-7.82; P=0.0001) after adjusting for age and sex. Our findings provide evidence of the role that LTL palys in the pathological mechanisms of AMD, mainly in the GA subgroup but not the CNV subgroup.

PMID: 26049047 [PubMed - as supplied by publisher]

Int J Clin Exp Pathol. 2015 Mar 1;8(3):3174-9. eCollection 2015.

Haplotypes of RHO polymorphisms and susceptibility to age-related macular degeneration.

Tang K, Wang W, Wang Q, Wang L, Bai H, Jiang Y, Huang Y.

OBJECTIVE: To investigate whether haplotypes of rhodopsin (RHO) polymorphisms including rs7984, rs2855552, rs2855557 and rs2410 were associated with age-related macular degeneration (AMD) risk in Chinese Han population.

METHODS: Genotypes of rs7984, rs2855552, rs2855557 and rs2410 were detected with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) in 186 cases and 196 healthy controls. Then, the haplotypes were established with Haploview 4.2 software. And the effects of clinical charactersitics on the frequency of GTTG haplotype were also analyzed. Odds ratios (ORs) with 95% confidence interval (95% CI) were utilized to assess the relationship of haplotypes and genotypes of RHO polymorphisms with susceptibility to AMD.

RESULTS: Genotype distribution of all polymorphisms in control group were all in agreement with Hardy-Weinberg equilibrium (HWE) (P>0.05). In the analysis, we found that mutant alleles of rs7984 and rs2855557 were both associated with increased risk of AMD. For genotype analysis, rs7984 AA and rs2855557AA, rs2410GG genotypes all could increase the risk for AMD (OR=1.905, 95% CI=1.143-3.174; OR=2.226, 95% CI=1.261-3.932; OR=2.073, 95% CI=1.105-3.888). However, rs2855552 showed no effects on the onset of AMD. Compared with GTTA, the haplotypes of GGTG, ATAA and GTTG were all related with AMD susceptibility. Further analysis suggested that age, hypertension and hyperlipidemia history play important roles in the frequency alteration of GTTG haplotype.

CONCLUSION: RHO polymorphisms (rs7984, rs2855557 and rs2410) and haplotypes may confer remarkable susceptibility to AMD. Further investigation showed that gene and environmental factors may work together in the pathogenesis of AMD.

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Am J Primatol. 2015 Jun 1. [Epub ahead of print]

Genetic studies on the Cayo Santiago rhesus macaques: A review of 40 years of research.

Widdig A, Kessler MJ, Bercovitch FB, Berard JD, Duggleby C, Nürnberg P, Rawlins RG, Sauermann U, Wang Q, Krawczak M, Schmidtke J.

Abstract: Genetic studies not only contribute substantially to our current understanding of the natural variation in behavior and health in many species, they also provide the basis of numerous in vivo models of human traits. Despite the many challenges posed by the high level of biological and social complexity, a long lifespan and difficult access in the field, genetic studies of primates are particularly rewarding because of the close evolutionary relatedness of these species to humans. The free-ranging rhesus macaque (Macaca mulatta) population on Cayo Santiago (CS), Puerto Rico, provides a unique resource in this respect because several of the abovementioned caveats are of either minor importance there, or lacking altogether, thereby allowing long-term genetic research in a primate population under constant surveillance since 1956. This review summarizes more than 40 years of genetic research carried out on CS, from early blood group typing and the genetic characterization of skeletal material via population-wide paternity testing with DNA fingerprints and short tandem repeats (STRs) to the analysis of the highly polymorphic DQB1 locus within the major histocompatibility complex (MHC). The results of the paternity studies also facilitated subsequent studies of male dominance and other factors influencing male reproductive success, of male reproductive skew, paternal kin bias, and mechanisms of paternal kin recognition. More recently, the CS macaques have been the subjects of functional genetic and gene expression analyses and have played an important role in behavioral and quantitative genetic studies. In addition, the CS colony has been used as a natural model for human adult-onset macular degeneration, glaucoma, and circadian rhythm disorder. Our review finishes off with a discussion of potential future directions of research on CS, including the transition from STRs to single nucleotide polymorphism (SNP) typing and whole genome sequencing.

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Invest Ophthalmol Vis Sci. 2015 Jun 1;56(6):3427-40.

A chimeric cfh transgene leads to increased retinal oxidative stress, inflammation, and accumulation of activated subretinal microglia in mice.

Aredo B, Li T, Chen X, Zhang K, Wang CX, Gou D, Zhao B, He Y, Ufret-Vincenty RL.

PURPOSE: Variants of complement factor H (Cfh) affecting short consensus repeats (SCRs) 6 to 8 increase the risk of age-related macular degeneration. Our aim was to explore the effect of expressing a Cfh variant on the in vivo susceptibility of the retina and RPE to oxidative stress and inflammation, using chimeric Cfh transgenic mice (chCfhTg).

METHODS: The chCfhTg and age-matched C57BL/6J (B6) mice were subjected to oxidative stress by either normal aging, or by exposure to a combination of oral hydroquinone (0.8% HQ) and increased light. Eyes were collected for immunohistochemistry of RPE-choroid flat mounts and of retinal sections, ELISA, electron microscopy, and RPE/microglia gene expression analysis.

RESULTS: Aging mice to 2 years led to an increased accumulation of basal laminar deposits, subretinal microglia/macrophages (MG/MΦ) staining for CD16 and for malondialdehyde (MDA), and MDA-modified proteins in the retina in chCfhTg compared to B6 mice. The chCfhTg mice maintained on HQ diet and increased light showed greater deposition of basal laminar deposits, more accumulation of fundus spots suggestive of MG/MΦ, and increased deposition of C3d in the sub-RPE space, compared to controls. In addition, chCfhTg mice demonstrated upregulation of NLRP3, IP-10, CD68, and TREM-2 in the RNA isolates from RPE/MG/MΦ.

CONCLUSIONS: Expression of a Cfh transgene introducing a variant in SCRs 6 to 8 was sufficient to lead to increased retinal/RPE susceptibility to oxidative stress, a proinflammatory MG/MΦ phenotype, and a proinflammatory RPE/MG/MΦ gene expression profile in a transgenic mouse model. Our data suggest that altered interactions of Cfh with MDA-modified proteins may be relevant in explaining the effects of the Cfh variant.

PMID: 26030099 [PubMed - in process]

Kaohsiung J Med Sci. 2015 Jun;31(6):309-14. Epub 2015 Apr 21.

The gene mutation in a Taiwanese family with X-linked retinoschisis.

Huang CT, Chen SP, Tsai RK.

Abstract: X-linked retinoschisis (XLRS) is one of the leading causes of macular degeneration in male children. The purpose of this study is to describe the clinical characteristics of a Taiwanese family with X-linked retinoschisis (XLRS) and to investigate the genetic mutation in the retinoschisin 1 (RS1) gene. A total of four participants in this XLRS family were analyzed. Complete ophthalmic examinations were performed, including best corrected visual acuity, optical coherence tomography (OCT), and electroretinogram (ERG). Direct DNA sequence of the RS1 gene identified one affected male and one female carrier. The affected male, had a cartwheel-like macular appearance and abnormal retinal pigment epithelium pigmentation in his bilateral eyes. The mixed scotopic ERG b-wave was more reduced than a-wave. OCT revealed typical macular microcystic schisis cavities. Direct DNA sequence analysis revealed a single base pair substitution in Exon 4, 304C > T, resulting in Arg102Trp. Our results show a RS1 (304C > T) mutation in a Taiwanese family with XLRS. This finding expands the clinical profiles of RS1 mutation and may help to further understand its pathogenesis.

PMID: 26043410 [PubMed - in process]

Diet, lifestyle and low vision

Clin Ophthalmol. 2015 May 15;9:873-6. eCollection 2015.

Pharmacogenetics and nutritional supplementation in age-related macular degeneration.

Hampton BM, Kovach JL, Schwartz SG.

Abstract: The Age-Related Eye Disease Study (AREDS) recommended treatment with antioxidants plus zinc in patients with intermediate or advanced age-related macular degeneration in order to reduce progression risks. Recent pharmacogenetic studies have reported differences in treatment outcomes with respect to variants in genes for CFH and ARMS2, although the treatment recommendations based on these differences are controversial. Different retrospective analyses of subsets of patients from the same AREDS trial have drawn different conclusions. The practicing clinician, who is not an expert on genetics, clinical trial design, or statistical analysis, may be uncertain how to interpret these results. Based on the balance of the available literature, we suggest not changing established practice recommendations until additional evidence from clinical trials becomes available.

PMID: 26028959 [PubMed] PMCID: PMC4440436

PLoS One. 2015 Jun 4;10(6):e0128395. eCollection 2015.

Dietary supplement enriched in antioxidants and omega-3 protects from progressive light-induced retinal degeneration.

Ramchani-Ben Othman K, Cercy C, Amri M, Doly M, Ranchon-Cole I.

Abstract: In the present study, we have evaluated one of the dietary supplements enriched with antioxidants and fish oil used in clinical care for patient with age-related macular degeneration. Rats were orally fed by a gastric canula daily with 0.2 ml of water or dietary supplement until they were sacrificed. After one week of treatment, animals were either sacrificed for lipid analysis in plasma and retina, or used for evaluation of rod-response recovery by electroretinography (ERG) followed by their sacrifice to measure rhodopsin content, or used for progressive light-induced retinal degeneration (PLIRD). For PLIRD, animals were transferred to bright cyclic light for one week. Retinal damage was quantified by ERG, histology and detection of apoptotic nuclei. Animals kept in dim-cyclic-light were processed in parallel. PLIRD induced a thinning of the outer nuclear layer and a reduction of the b-wave amplitude of the ERG in the water group. Retinal structure and function were preserved in supplemented animals. Supplement induced a significant increase in omega-3 fatty acids in plasma by 168% for eicosapentaenoic acid (EPA), 142% for docosapentaenoic acid (DPA) and 19% for docosahexaenoic acid (DHA) and a decrease in the omega-6 fatty acids, DPA by 28%. In the retina, supplement induced significant reduction of linolenic acid by 67% and an increase in EPA and DPA by 80% and 72%, respectively, associated with significant decrease in omega-6 DPA by 42%. Supplement did not affect rhodopsin content or rod-response recovery. The present data indicate that supplement rapidly modified the fatty acid content and induced an accumulation of EPA in the retina without affecting rhodopsin content or recovery. In addition, it protected the retina from oxidative stress induced by light. Therefore, this supplement might be beneficial to slow down progression of certain retinal degeneration.

PMID: 26042773 [PubMed - in process]

Ophthalmologe. 2015 Jun 4. [Epub ahead of print]

[Requirements for low vision magnification aids in age-related macular degeneration : Data from the Tübingen low vision clinic (comparison of 2007-2011 with 1999-2005)].[Article in German]

Altpeter EK, Nguyen NX.

BACKGROUND: The purpose of this study was to investigate if there has been a change in requirements for low vision magnification aids in recent years.

PATIENTS AND METHODS: The collective data from age-related macular degeneration (AMD) patients from the Tübingen low vision clinic from the years 2007-2011 were compared with the patient collective from the years 1999-2005. Magnification needs and the prescribed magnifying aids for reading in the categories magnifying spectacles, hand-held magnifiers, monocular telescopes, electronic magnifiers and

electronic reading devices were evaluated. In addition patients from 2010 and 2011 were divided into dry and neovascular AMD and the prescribed magnification aids were compared for these AMD forms.

RESULTS: There was no significant change in in the prescribed magnification reading aids for AMD patients between the years 1999-2005 and 2007-2011. An electronic magnifier was prescribed most often (both collectives 43 %), followed by hand-held magnifiers (32 and 29.5 %, respectively) and magnifying spectacles (17 and 18.8 %, respectively). Also the magnifying needs and mean age of the AMD patients did not change significantly between the two periods (2007-2011 versus 1999-2005). The detailed analysis for dry and neovascular AMD for the years 2010 and 2011 showed no significant differences for the most commonly prescribed low vision aids. The prescription of low vision aids is not influenced by the AMD classification (dry or neovascular), only by the magnification needs.

CONCLUSION: There is an unchanged and still high demand for rehabilitation aids of AMD patients, for dry as well as for neovascular AMD even after the introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy.

PMID: 26040791 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2015 Jun;50(3):225-9.

SKread predicts handwriting performance in patients with low vision.

Downes K, Walker LL, Fletcher DC.

OBJECTIVE: To assess whether performance on the Smith-Kettlewell Reading (SKread) test is a reliable predictor of handwriting performance in patients with low vision.

DESIGN: Cross-sectional study.

PARTICIPANTS: Sixty-six patients at their initial low-vision rehabilitation evaluation.

METHODS: The patients completed all components of a routine low-vision appointment including logMAR acuity, performed the SKread test, and performed a handwriting task. Patients were timed while performing each task and their accuracy was recorded. The handwriting task was performed by having patients write 5 5-letter words into sets of boxes where each letter is separated by a box. The boxes were 15 × 15 mm, and accuracy was scored with 50 points possible from 25 letters: 1 point for each letter within the confines of a box and 1 point if the letter was legible. Correlation analysis was then performed.

RESULTS: Median age of participants was 84 (range 54-97) years. Fifty-seven patients (86%) had age-related macular degeneration or some other maculopathy, whereas 9 patients (14%) had visual impairment from media opacity or neurologic impairment. Median Early Treatment Diabetic Retinopathy Study acuity was 20/133 (range 20/22 to 20/1000), and median logMAR acuity was 0.82 (range 0.04-1.70). SKread errors per block correlated with logMAR acuity ($r = 0.6$), and SKread time per block correlated with logMAR acuity ($r = 0.51$). SKread errors per block correlated with handwriting task time/accuracy ratio ($r = 0.61$). SKread time per block correlated with handwriting task time/accuracy ratio ($r = 0.7$). LogMAR acuity score correlated with handwriting task time/accuracy ratio ($r = 0.42$). All p values were < 0.01.

CONCLUSIONS: SKread scores predict handwriting performance in patients with low vision better than logMAR acuity.

PMID: 26040223 [PubMed - in process]