

Issue 165

Tuesday 28 January, 2014

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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Drug treatment

JAMA Ophthalmol. 2014 Jan 23. doi: 10.1001/jamaophthalmol.2013.7647. [Epub ahead of print]

The Effects of Technological Advances on Outcomes for Elderly Persons With Exudative Age-related Macular Degeneration.

Sloan FA, Hanrahan BW.

IMPORTANCE: Exudative age-related macular degeneration (ARMD) is the major cause of blindness among US elderly. Developing effective therapies for this disease has been difficult.

OBJECTIVES: To assess the effects of introducing new therapies for treating exudative ARMD on vision of the affected population and other outcomes among Medicare beneficiaries newly diagnosed as having ARMD.

DESIGN: The study used data from a 5% sample of Medicare claims and enrollment data with a combination of a regression discontinuity design and propensity score matching to assess the effects on the introduction or receipt of new technologies on study outcomes during a 2-year follow-up period.

SETTING AND PARTICIPANTS: The analysis was based on longitudinal data for the United States, January 1, 1994, to December 31, 2011, for Medicare beneficiaries with fee-for-service coverage. The sample was limited to beneficiaries 68 years or older newly diagnosed as having exudative ARMD as indicated by beneficiaries having no claims with this diagnosis in a 3-year look-back period.

EXPOSURES: The comparisons with vision outcomes were after vs before the introduction of photodynamic therapy and anti-vascular endothelial growth factor (VEGF) therapy. The comparisons for depression and long-term care facility admission were between beneficiaries newly diagnosed as having exudative ARMD who received photodynamic therapy or anti-VEGF therapy compared with beneficiaries having the diagnosis who received no therapy for this disease.

MAIN OUTCOMES AND MEASURES: Onset of decrease in vision, vision loss or blindness, depression, and admission to a long-term care facility.

RESULTS: Among beneficiaries newly diagnosed as having exudative ARMD, the introduction of anti-VEGF therapy reduced vision loss by 41% (95% CI, 52%-68%) and onset of severe vision loss and blindness by 46% (95% CI, 47%-63%). Such beneficiaries who received anti-VEGF therapy and were not admitted to a long-term care facility during the look-back period were 19% (95% CI, 72%-91%) less likely on average to be admitted to a long-term care facility during the follow-up period.

CONCLUSIONS AND RELEVANCE: This study demonstrates gains in population vision from the introduction of anti-VEGF therapy for patients 68 years or older with an exudative ARMD diagnosis in

community-based settings in the United States.

PMID: 24458013 [PubMed - as supplied by publisher]

Retina. 2014 Jan 22. [Epub ahead of print]

DIAMETER OF RETINAL VESSELS IN PATIENTS WITH DIABETIC MACULAR EDEMA IS NOT ALTERED BY INTRAVITREAL RANIBIZUMAB (LUCENTIS).

Terai N, Haustein M, Siegel A, Stodtmeister R, Pillunat LE, Sandner D.

PURPOSE: To investigate the effect(s) of intravitreally injected ranibizumab on retinal vessel diameter in patients with diabetic macular edema.

METHODS: Participants of this prospective study were 14 men and 16 women (30 eyes) aged 60 ± 11 years (mean $\pm$ standard deviation), all with clinically significant diabetic macular edema. Treatment comprised 3 intravitreal injections of ranibizumab given at 4-week intervals. Examinations were conducted before the first (baseline), before the second (Month 1), before the third (Month 2) injections, and 3 months after baseline (Month 3). Measured parameters included systemic blood pressure, static retinal vessel analysis (central retinal artery equivalent and central retinal vein equivalent), and dynamic retinal vessel analysis, as measured by the change in vessel diameter in response to flicker stimulation during three measurement cycles. Flicker stimulation was accomplished using a 50-second baseline recording, followed by an online measurement during 20-second flicker stimulation and 80-second online measurements in both arteriolar and venular vessel segments.

RESULTS: Static retinal vessel analysis showed a reduction of central retinal artery equivalent from $186.25 \pm 51.40 \mu\text{m}$ (baseline) to $173.20 \pm 22.2 \mu\text{m}$ (Month 1), to $174.30 \pm 27.30 \mu\text{m}$ (Month 2), and to $170.56 \pm 22.89 \mu\text{m}$ (Month 3), none of which was statistically significant ($P = 0.23, 0.12, \text{ and } 0.14$, respectively). Central retinal vein equivalent was reduced from $216.21 \pm 25.0 \mu\text{m}$ (baseline) to $214.48 \pm 25.4 \mu\text{m}$ (Month 1), to $214.80 \pm 24.30 \mu\text{m}$ (Month 2), and to $211.41 \pm 24.30 \mu\text{m}$ (Month 3), revealing no statistically significant differences between examination time points ($P = 0.54, 0.06, \text{ and } 0.24$, respectively). Dynamic vessel analysis yielded a mean retinal arterial diameter change of $+1.47\% \pm 2.3$ (baseline), $+1.91\% \pm 2.5$ (Month 1), $+1.76\% \pm 2.2$ (Month 2), and $+1.66\% \pm 2.1$ (Month 3), none of which showed statistically significant differences ($P = 0.32, 0.49, \text{ and } 0.70$, respectively). Mean retinal venous diameter changes were $+3.15\% \pm 1.7$ (baseline), $+3.7\% \pm 2.3$ (Month 1), $+4.0\% \pm 2.0$ (Month 2), and $+4.95\% \pm 1.9$ (Month 3), none of which showed statistically significant differences ($P = 0.12, 0.17, \text{ and } 0.14$, respectively). Central retinal thickness, as measured by spectral domain optical coherence tomography, decreased significantly from $435.2 \pm 131.8 \mu\text{m}$ (baseline) to $372.3 \pm 142.8 \mu\text{m}$ (Month 3), $P = 0.01$. Regression analysis of arteriolar and venular diameters indicated that there was no significant correlation between these 2 parameters ($r = 0.053$; $P = 0.835$ and $r = 0.06$; $P = 0.817$, respectively). Also, no significant correlation was observed between the difference in the central retinal thickness and change in arteriolar or venular dilatation ($r = 0.291$, $P = 0.241$ and $r = 0.06$, $P = 0.435$, respectively).

CONCLUSION: Intravitreally applied ranibizumab did not significantly affect retinal vessel diameter in patients with diabetic macular edema. Decline in the central foveal thickness after ranibizumab therapy, as measured by spectral domain optical coherence tomography, was not linked to any change in retinal vessel diameter or dilatatory response, neither for arterioles nor venules.

PMID: 24457978 [PubMed - as supplied by publisher]

Digit J Ophthalmol. 2013 Dec 30;19(4):59-63. doi: 10.5693/djo.02.2013.09.001. eCollection 2013.

Value of anti-VEGF treatment in choroidal neovascularization associated with autosomal recessive bestrophinopathy.

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Madhusudhan S, Hussain A, Sahni JN.

Abstract: A 26-year-old white woman presented with a 1-year history of reduced vision in both eyes, bilateral yellowish deposits in the central macula, and pale yellow retinal flecks extending to midretinal periphery. Choroidal neovascularization (CNV) was confirmed in her left eye. On optical coherence tomography, both eyes showed diffuse intraretinal cystic spaces, thickening and separation of the photoreceptor layer from the retinal pigment epithelium (RPE), subretinal fluid, and focal thickening at the level of the RPE at the fovea. A diagnosis of autosomal recessive bestrophinopathy was confirmed by electrodiagnostic and molecular genetics testing. The CNV responded well to intravitreal ranibizumab therapy, and visual acuity in the left eye improved and stabilized; however, retinoschisis due to fluctuations in intraretinal fluid persisted. This case highlights the fact that current optical coherence tomography-driven protocols used widely to treat neovascular age-related macular degeneration may not be appropriate for CNV associated with other retinal diseases.

PMID: 24459458 [PubMed - in process]

ScientificWorldJournal. 2013 Dec 24;2013:958724. doi: 10.1155/2013/958724. eCollection 2013.

The role of epiretinal membrane on treatment of neovascular age-related macular degeneration with intravitreal bevacizumab.

Alkin Z1, Ozkaya A1, Osmanbasoglu OA1, Agca A1, Karakucuk Y1, Yazici AT1, Demirok A2.

Author information

Purpose: To determine the effect of epiretinal membranes (ERM) on the treatment response and the number of intravitreal bevacizumab injections (IVB) in patients with neovascular age-related macular degeneration (nAMD).

Methods: A retrospective chart review was performed on 63 eyes of 63 patients. The patients were divided into AMD group (n = 35) and AMD/ERM group (n = 28). Best corrected visual acuity (BCVA) and central retinal thickness (CRT), as well as the number of injections, were evaluated.

Results: There was a significant improvement in BCVA at 3 months for the AMD and AMD/ERM groups (P = 0.02, P = 0.03, resp.). At 6, 12, and 18 months, BCVA did not change significantly in either of the groups compared to baseline (P > 0.05 for all). At 3, 6, 12, and 24 months, the AMD group had an improvement in BCVA (logMAR) of 0.09, 0.06, 0.06, and 0.03 versus 0.08, 0.07, 0.05, and 0.03 for the AMD/ERM group (P = 0.29, P = 0.88, P = 0.74, P = 0.85, resp.). A significant decrease in CRT occurred in both groups for all time points (P < 0.001 for all). The change in CRT was not statistically different between the two groups at all time points (P > 0.05 for all). The mean number of injections over 24 months was 8.8 in the AMD group and 9.2 in the AMD/ERM group (P = 0.76).

Conclusion: During 24 months, visual and anatomical outcomes of IVB in nAMD patients were comparable with those in nAMD patients with ERM with similar injection numbers.

PMID: 24453930 [PubMed - in process]

Clin Interv Aging. 2014;9:141-5. doi: 10.2147/CIA.S56863. Epub 2014 Jan 10.

Visual outcome of intravitreal ranibizumab for exudative age-related macular degeneration: timing and prognosis.

Canan H1, Sizmaz S2, Altan-Yaycioglu R1, Saritürk C3, Yilmaz G4.

PURPOSE: To describe 1-year clinical results of intravitreal ranibizumab treatment in patients with

choroidal neovascularization secondary to exudative age-related macular degeneration (AMD) and to evaluate whether early treatment is a predictive value for prognosis of the disease.

MATERIALS AND METHODS: Clinical records were retrospectively reviewed of 104 eyes that underwent intravitreal ranibizumab therapy for exudative AMD. Patients were divided into two groups according to their symptom duration: group 1, <1 month; and group 2, 1-3 months. After three monthly injections, patients were examined monthly, and subsequent injections were performed as needed.

RESULTS: There were 43 female (48.9%) and 45 males (51.1%). The follow-up time was 13.7 ± 1.9 (12-19) months. The mean logarithm of minimum angle of resolution best-corrected visual acuity (BCVA) improved significantly, from 0.45 ± 0.639 at baseline to 0.08 ± 0.267 at 12 months in group 1, and from 1.06 ± 0.687 at baseline to 0.75 ± 0.563 at 12 months in group 2. The increase in BCVA was statistically significant in group 1 ($P=0.009$). The mean central retinal thickness (CRT) decreased significantly, from 355.13 ± 119.93 μm at baseline to 250.85 ± 45.48 μm at 12 months in group 1, and from 371.88 ± 91.047 μm at baseline to 268.61 ± 53.51 μm at 12 months in group 2. The decrease in CRT was statistically significant in group 1 ($P=0.001$).

CONCLUSION: Intravitreal ranibizumab therapy was effective in significantly increasing mean BVCA and reducing CRT. Shorter duration of AMD, as measured by the subjective duration of visual symptoms, is associated with better visual outcome after treatment.

PMID: 24453484 [PubMed - in process]

Retina. 2014 Jan 21. [Epub ahead of print]

EXACERBATION OF CHOROIDAL AND RETINAL PIGMENT EPITHELIAL ATROPHY AFTER ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Young M, Chui L, Fallah N, Or C, Merkur AB, Kirker AW, Albani DA, Forooghian F.

PURPOSE: To study the progression of retinal pigment epithelium (RPE) and choroidal atrophy in patients with neovascular age-related macular degeneration (AMD) and to assess for a possible association with the number and type of anti-vascular endothelial growth factor treatments.

METHODS: Patients with neovascular AMD and a minimum of 1-year follow-up were reviewed. Fellow eyes with nonneovascular AMD were used as control eyes. Retinal pigment epithelial atrophy area and choroidal thickness were determined using spectral-domain optical coherence tomography. Multivariable regression models were used for statistical analyses.

RESULTS: A total of 415 eyes were included in the study, with a mean follow-up of 2.2 years. Eyes with neovascular AMD had greater progression of RPE atrophy and choroidal atrophy compared with those with nonneovascular AMD ($P < 0.001$). Progression of RPE atrophy and choroidal atrophy was independently associated with the total number of injections of bevacizumab and ranibizumab (all P values ≤ 0.001). In the subgroup of 84 eyes with neovascular AMD and without RPE atrophy at baseline, only bevacizumab was associated with the progression of RPE atrophy ($P = 0.003$). This study likely lacked statistical power to detect an association with ranibizumab in this subgroup.

CONCLUSION: Retinal pigment epithelial atrophy and choroidal atrophy in neovascular AMD seem to be exacerbated by anti-vascular endothelial growth factor treatment. Possible differences between bevacizumab and ranibizumab require further investigation.

PMID: 24451923 [PubMed - as supplied by publisher]

Int J Mol Sci. 2014 Jan 22;15(1):1606-24. doi: 10.3390/ijms15011606.

Intravitreal Injection of Ranibizumab and CTGF shRNA Improves Retinal Gene Expression and Microvessel Ultrastructure in a Rodent Model of Diabetes.

Hu B1, Zhang Y2, Zeng Q3, Han Q4, Zhang L5, Liu M6, Li X7.

Abstract: Therapeutic modalities targeting vascular endothelial growth factor (VEGF) have been used to treat neovascularization and macular edema. However, anti-VEGF treatment alone may cause up-regulation of connective tissue growth factor (CTGF) in the retina, increasing the risk of fibrosis and tractional retinal detachment. Therefore, in this study, we employ a novel dual-target intervention that involves intravitreal injection of the VEGF inhibitor ranibizumab and a transfection reagent-treated non-viral vector carrying anti-CTGF short hairpin RNA (shRNA) driven by human RNA polymerase III promoter U6. The effects of the dual-target intervention on the expression of VEGF and CTGF and on microvessel ultrastructure were examined in retina of streptozocin-induced diabetic rats. CTGF was significantly up-regulated at week 8 after diabetic induction, whereas VEGF was not up-regulated until week 10. The high expression of both genes was maintained at week 12. Transmission electron microscopy also revealed progressive exacerbation of microvessel ultrastructure during the same period. In addition, ranibizumab significantly lowered VEGF but elevated CTGF mRNA, whereas CTGF shRNA significantly reduced the mRNA levels of both CTGF and VEGF in diabetic retinas. Importantly, dual-target intervention normalized the transcript levels of both target genes and ameliorated retinal microvessel ultrastructural damage better than either single-target intervention. These results suggest the advantages of dual-target over single-target interventions in diabetic retina and reveal a novel therapeutic modality for diabetic retinopathy.

PMID: 24451141 [PubMed - in process]

BMC Ophthalmol. 2014 Jan 21;14(1):7. [Epub ahead of print]

Efficacy and safety of widely used treatments for macular oedema secondary to retinal vein occlusion: a systematic review.

Glanville J, Patterson J, McCool R, Ferreira A, Gairy K, Pearce I.

BACKGROUND: Macular oedema secondary to retinal vein occlusion (RVO) can cause vision loss due to blockage of the central retinal vein (CRVO) or a branch retinal vein (BRVO). This systematic review assessed the efficacies of widely used treatments for macular oedema secondary to RVO and the feasibility of conducting indirect comparisons between these therapies.

METHODS: A systematic review was undertaken in November 2010, including a literature search for trials in medical databases and relevant websites. Abstracts, conference presentations and unpublished studies were considered. Studies were data-extracted and quality assessed by two independent researchers. Outcome measures included the mean change in best corrected visual acuity (BCVA) from baseline in the study eye and/or number of patients gaining at least 10 letters from baseline to 6 months or the nearest equivalent time point.

RESULTS: Fourteen unique randomized controlled trials (RCTs) were identified. Ranibizumab 0.5 mg produced greater improvements in BCVA at 6 months than sham in BRVO (mean difference 11.0 letters, 95% confidence interval [CI] 7.83, 14.17) and CRVO (mean difference 14.10 letters, 95% CI 10.51, 17.69) in two double-blind sham-controlled RCTs. Pooled data from two double-blind, sham-controlled RCTs showed that improvements in BCVA were also significantly better for dexamethasone intravitreal (IVT) implant 0.7 mg compared with sham in patients with BRVO or CRVO (mean difference 2.5 letters, 95% CI 0.7, 4.3); the difference was significant for BRVO alone, but not CRVO alone. A significantly greater proportion of patients with BRVO gained ≥ 15 letters with laser therapy vs. no treatment at 36 months in a large prospective RCT (odds ratio 3.16, 95% CI 1.25, 8.00), whereas no difference was observed at 9 months in a smaller study. Three studies reported no benefit for laser therapy in CRVO. No indirect

comparisons with ranibizumab were feasible due to differences in study design and baseline characteristics.

CONCLUSIONS: Data from RCTs for ranibizumab and dexamethasone IVT demonstrate that both new agents constitute significant improvements over the previously widely accepted standard of care (laser therapy) for the treatment of BRVO and CRVO. However, head-to-head studies are needed to assess the relative efficacies of licensed therapies for RVO.

PMID: 24447389 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Jan 16. pii: S0161-6420(13)01105-6. doi: 10.1016/j.optha.2013.11.026. [Epub ahead of print]

Refractive Changes after Pharmacologic Resolution of Diabetic Macular Edema.

Deák GG1, Lammer J1, Prager S1, Mylonas G1, Bolz M1, Schmidt-Erfurth U2; Diabetic Retinopathy Research Group Vienna.

PURPOSE: To determine precisely the mean change in refractive power induced by treatment in patients with diabetic macular edema (DME).

DESIGN: Prospective, randomized study.

PARTICIPANTS: Fifty eyes of 50 consecutive patients with clinically significant macular edema receiving all 3 types of current state-of-the-art treatment with intravitreal antiedematous substances (ranibizumab, bevacizumab, or triamcinolone).

METHODS: Patients were followed up at monthly intervals and were treated following a standardized pro re nata regimen according to protocol. Best-corrected visual acuity (BCVA) was determined by certified visual acuity examiners. The refractive power of the treated eyes was determined using a push-plus technique. The change in refraction between baseline and the visit when the macula was completely dry or when the central subfield thickness (CST) measured by optical coherence tomography had reached the thinnest level was analyzed.

MAIN OUTCOME MEASURES: Spherical equivalent refraction (SER) and CST.

RESULTS: Fifty eyes of 50 patients received intravitreal therapy using ranibizumab (n = 11), bevacizumab (n = 20), or triamcinolone (n = 19). Mean BCVA was 0.33 ± 0.23 logarithm of the minimum angle of resolution (logMAR) and mean CST was 492 ± 130 μ m. The mean SER was 0.41 ± 2.06 diopters (D) at baseline. The BCVA at the time of optimal retinal morphologic features was 0.24 ± 0.2 logMAR, mean CST was 300 ± 78 μ m, and mean change in SER was -0.01 ± 0.46 D. Changes in BCVA and CST were statistically significant ($P < 0.0001$), but the SER change was not ($P = 0.824$).

CONCLUSIONS: Appropriate spectacle correction can be prescribed to patients with DME any time during ongoing therapy using antiedematous substances because resolution of retinal thickening is not associated with an increased risk of a myopic shift.

PMID: 24439462 [PubMed - as supplied by publisher]

Cesk Slov Oftalmol. 2013 Aug;69(3):96-101.

[Wet form age-related macular degeneration two years treatment results using anti VEGF drugs]. [Article in Czech]

Studnička J, Rencová E, Dusová J, Marák J, Burova M, Rozsival P, Jarkovský J, Kandrnl V.

Aim: The aim of the study was to establish the efficacy of anti VEGF (Vascular Endothelial Growing Factor) drugs in the treatment of wet form ARMD (Age-Related Macular Degeneration) in everyday clinical practice in the Department of Ophthalmology, Faculty Hospital, Hradec Králové, Czech Republic, E.U., in patients registered in the Czech national registry AMADEUS.

Material and methods: Retrospective study with 24 months follow-up period. In the group were evaluated 143 eyes of 140 patients, out of them were 77 women (65.8 %), of average age 73.09 (71.69 - 74.48) years, and 40 men (34.2 %) of average age 74 (58 - 85) years. All of the patients were completely examined before the beginning of the treatment; during the treatment were, except the standardized eye examination, in patients treated with ranibizumab the color fundus photography and Optical Coherence Tomography (OCT) with measuring of the central retinal thickness performed every three months at least. The patients treated by pegaptanib were examined every six weeks before the drug application. The fluorescence angiography (FA) was performed at the beginning of the treatment to establish the type and extension of the choroidal neovascularization and during the treatment in case of necessity to establish the activity of the choroidal neovascular membrane (CNV). The treatment by ranibizumab was in the regimen PRN (pro re nata), and pegaptanib was applied every six months during the first year with the follow-up evaluation of the findings. The treatment evaluations were performed at 12 and 24 months.

Results: During the two years follow - up period, the authors noticed in patients treated with ranibizumab loss of 5.12 letters of ETDRS optotypes in case of mostly classical CNV, in occult CNV loss of 5.45 letters, and in minimally classical CNV loss of 2.83 letters. In three evaluated eyes with classical CNV in patients treated with pegaptanib we noticed after 2 years loss of 6.67 letters, in eleven eyes with occult CNV we established loss of 9.91 letters, and in two eyes with minimally classical CNV the average best-corrected visual acuity (BCVA) remained unchanged. The pegaptanib treatment results may be influenced by small number of evaluated patients. The visual acuity changes during the two years treatment were not statistically significant. We noticed the decrease of average CRT (central retinal thickness) in all types of CNV treated both with ranibizumab and pegaptanib after the two years follow up. To reach these results, an average of 5.51 applications of ranibizumab and 9 applications of pegaptanib during the two years were used.

Conclusion: In the followed-up group we found, comparing to the natural course of neovascular form of ARMD, retarding of the BCVA decrease during the two years treatment with VEGF inhibitors in everyday clinical practice. Better results were achieved with ranibizumab treatment, however the differences were not statistically significant. **Key words:** age related macular degeneration, AMADEUS Czech national registry, ranibizumab, pegaptanib.

PMID: 24437955 [PubMed - in process]

Adv Ther. 2014 Jan 18. [Epub ahead of print]

Erratum to: Retrospective Analysis of First-Line Anti-Vascular Endothelial Growth Factor Treatment Patterns in Wet Age-Related Macular Degeneration.

Johnston SS, Wilson K, Huang A, Smith D, Varker H, Turpcu A.

PMID: 24442833 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2014 Feb;92(1):98. doi: 10.1111/aos.12337.

Implementation studies of ranibizumab for neovascular age-related macular degeneration.

Bloch SB.

PMID: 24447787 [PubMed - in process]

Other treatment & diagnosis

Eye (Lond). 2014 Jan 24. doi: 10.1038/eye.2013.275. [Epub ahead of print]

Predictors for the progression of geographic atrophy in patients with age-related macular degeneration: fundus autofluorescence study with modified fundus camera.

Jeong YJ1, Hong IH1, Chung JK1, Kim KL1, Kim HK1, Park SP2.

Purpose: We examined the association between abnormal fundus autofluorescence (FAF) features on images obtained by a modified fundus camera (mFC) and geographic atrophy (GA) progression in patients with age-related macular degeneration (AMD).

Methods: Serial FAF images of 131 eyes from 131 patients with GA were included in the study. All FAF images were obtained with an mFC (excitation, ~500-610 nm; emission, ~675-715 nm). The GA area was quantified at baseline and 1 year later using a customized segmentation program. The yearly GA enlargement rate was then calculated. Abnormal FAF patterns in the junctional zone of GA were classified as None or Minimal change, Focal, Patchy, Banded, or Diffuse according to previously published classification based on confocal scanning laser ophthalmoscopy (cSLO). The relationship between GA enlargement and abnormal FAF was evaluated.

Results: The mean rate of GA enlargement was the fastest in eyes with Diffuse pattern (1.74 mm² per year), followed by eyes with the Banded pattern (1.69 mm² per year). Binary logistic regression analysis revealed that eyes with the Banded and Diffuse pattern had significantly higher risk for GA enlargement compared with eyes with the other patterns.

Conclusions: FAF image obtained by mFC appears to be acceptable for evaluating GA in accordance with an established cSLO-based classification. Eyes with the Banded or the Diffuse patterns of abnormal FAF at baseline indicate a high risk for GA progression. Identifying patients at high risk for GA progression using an mFC is broadly available method that can provide additional information to help predict disease course. Eye advance online publication, 24 January 2014; doi:10.1038/eye.2013.275.

PMID: 24458203 [PubMed - as supplied by publisher]

J Ophthalmol. 2013;2013:135798. doi: 10.1155/2013/135798. Epub 2013 Dec 18.

Long-term outcomes of rheohaemapheresis in the treatment of dry form of age-related macular degeneration.

Studnička J1, Rencová E1, Bláha M2, Rozsival P1, Lánská M2, Bláha V3, Němčanský J4, Langrová H1.

Purpose: Determining long-term effects of rheohaemapheresis on the dry form of age-related macular degeneration.

Methods: This study evaluates 19 patients, average age of 67.6 years, treated with rheohaemapheresis and 18 patients, average age of 72.8 years, comprising the control group. Minimum follow up period was 3.5 years. Each treated patient received a series of 8 sessions of rheohaemapheresis of 1.5 plasma volumes within 10 weeks. We measured the drusenoid pigment epithelium detachment (DPED), best-corrected visual acuity (BCVA), electroretinography (ERG), and rheological parameters.

Results: In the treatment group, the baseline BCVA was 0.74 (0.36-1.0) 95% CI and BCVA after 3.5 years was 0.79 (0.41-1.0) 95% CI (P = 0.726). In the control group, the baseline BCVA was 0.71 (0.15-1.0) 95% CI and BCVA after 3.5 years decreased to 0.7 (0.32-0.87) 95% CI (P = 0.031). Baseline DPED was 6.78 ± 3.79 mm(2); after 3.5 years, it decreased to 4.13 ± 3.84 mm(2) (P < 0.001). In the control group, the baseline DPED was 4.09 ± 3.48 mm(2); after 3.5 years, it increased to 6.69 ± 4.2 mm(2) (P = 0.001). We noted increasing levels of positive wave peaking at 50 milliseconds (P50) after treatment (P = 0.022) and a

stable amplitude of photopic responses of treated patients.

Conclusion: Over the long term, rheohaemapheresis reduced the DPED, improved the function of photoreceptors, and prevented the decline of BCVA.

PMID: 24455194 [PubMed]

PLoS One. 2014 Jan 14;9(1):e85336. doi: 10.1371/journal.pone.0085336. eCollection 2014.

Tumorigenicity Studies of Induced Pluripotent Stem Cell (iPSC)-Derived Retinal Pigment Epithelium (RPE) for the Treatment of Age-Related Macular Degeneration.

Kanemura H1, Go MJ2, Shikamura M2, Nishishita N2, Sakai N3, Kamao H4, Mandai M3, Morinaga C3, Takahashi M3, Kawamata S1.

Abstract: Basic studies of human pluripotential stem cells have advanced rapidly and stem cell products are now seeing therapeutic applications. However, questions remain regarding the tumorigenic potential of such cells. Here, we report the tumorigenic potential of induced pluripotent stem cell (iPSC)-derived retinal pigment epithelium (RPE) for the treatment of wet-type, age-related macular degeneration (AMD). First, immunodeficient mouse strains (nude, SCID, NOD-SCID and NOG) were tested for HeLa cells' tumor-forming capacity by transplanting various cell doses subcutaneously with or without Matrigel. The 50% Tumor Producing Dose (TPD50 value) is the minimal dose of transplanted cells that generated tumors in 50% of animals. For HeLa cells, the TPD50 was the lowest when cells were embedded in Matrigel and transplanted into NOG mice (TPD50=10(1.1), n=75). The TPD50 for undifferentiated iPSCs transplanted subcutaneously to NOG mice in Matrigel was 10(2.12); (n=30). Based on these experiments, 1×10^6 iPSC-derived RPE were transplanted subcutaneously with Matrigel, and no tumor was found during 15 months of monitoring (n=65). Next, to model clinical application, we assessed the tumor-forming potential of HeLa cells and iPSC 201B7 cells following subretinal transplantation of nude rats. The TPD50 for iPSCs was 10(4.73) (n=20) and for HeLa cells 10(1.32) (n=37) respectively. Next, the tumorigenicity of iPSC-derived RPE was tested in the subretinal space of nude rats by transplanting $0.8-1.5 \times 10^4$ iPSC-derived RPE in a collagen-lined (1 mm×1 mm) sheet. No tumor was found with iPSC-derived RPE sheets during 6-12 months of monitoring (n=26). Considering the number of rodents used, the monitoring period, the sensitivity of detecting tumors via subcutaneous and subretinal administration routes and the incidence of tumor formation from the iPSC-derived RPE, we conclude that the tumorigenic potential of the iPSC-derived RPE was negligible.

PMID: 24454843 [PubMed - in process]

Biomaterials. 2014 Jan 15. pii: S0142-9612(13)01565-2. doi: 10.1016/j.biomaterials.2013.12.069. [Epub ahead of print]

Enhancement of retinal pigment epithelial culture characteristics and subretinal space tolerance of scaffolds with 200 nm fiber topography.

Liu Z1, Yu N2, Holz FG1, Yang F2, Stanzel BV3.

Abstract: Tissue engineered retinal pigment epithelial (RPE) transplantation is a promising cell-based therapy for age-related macular degeneration. The aim of this work is to develop a supportive scaffold with a favorable topography to aid functional RPE monolayer maintenance while being tolerated underneath the retina. To this end, films and electrospun substrates with fiber diameters ranging from 200 to 1000 nm were made of polyethylene terephthalate or poly(l-lactide-co-ε-caprolactone), and then tested using human fetal RPE cells in vitro and transplanted subretinally in rabbits. The results indicated that RPE on both 200 nm fiber variants showed the highest cell densities, adherent monolayers achieved deeper pigmentation, and more uniform hexagonal tight junctions. Facile subretinal implantation of flat 200 nm fiber membranes was

achieved by electrospinning them onto a porous rigid-elastic carrier. Spectral-domain optical coherence tomography showed a reattached, slightly thinned retina overlying the implants over 2 weeks observation. Histology demonstrated native RPE variably migrated onto the nanofibers, and a reactive gliosis with some photoreceptor degeneration. In conclusion, scaffolds with 200 nm fiber topography enhanced RPE culture, showed subretinal biocompatibility, and should thus be considered for future cell-based therapies in blinding retinal diseases.

PMID: 24439407 [PubMed - as supplied by publisher]

Lancet. 2014 Jan 15. pii: S0140-6736(13)62117-0. doi: 10.1016/S0140-6736(13)62117-0. [Epub ahead of print]

Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial.

Maclaren RE1, Groppe M2, Barnard AR3, Cottriall CL4, Tolmachova T5, Seymour L6, Clark KR7, During MJ8, Cremers FP9, Black GC10, Lotery AJ11, Downes SM12, Webster AR13, Seabra MC14.

BACKGROUND: Choroideremia is an X-linked recessive disease that leads to blindness due to mutations in the CHM gene, which encodes the Rab escort protein 1 (REP1). We assessed the effects of retinal gene therapy with an adeno-associated viral (AAV) vector encoding REP1 (AAV.REP1) in patients with this disease.

METHODS: In a multicentre clinical trial, six male patients (aged 35-63 years) with choroideremia were administered AAV.REP1 ($0.6\text{--}1.0 \times 10^{10}$ genome particles, subfoveal injection). Visual function tests included best corrected visual acuity, microperimetry, and retinal sensitivity tests for comparison of baseline values with 6 months after surgery. This study is registered with ClinicalTrials.gov, number NCT01461213.

FINDINGS: Despite undergoing retinal detachment, which normally reduces vision, two patients with advanced choroideremia who had low baseline best corrected visual acuity gained 21 letters and 11 letters (more than two and four lines of vision). Four other patients with near normal best corrected visual acuity at baseline recovered to within one to three letters. Mean gain in visual acuity overall was 3.8 letters (SE 4.1). Maximal sensitivity measured with dark-adapted microperimetry increased in the treated eyes from 23.0 dB (SE 1.1) at baseline to 25.3 dB (1.3) after treatment (increase 2.3 dB [95% CI 0.8-3.8]). In all patients, over the 6 months, the increase in retinal sensitivity in the treated eyes (mean 1.7 [SE 1.0]) was correlated with the vector dose administered per mm² of surviving retina ($r=0.82$, $p=0.04$). By contrast, small non-significant reductions ($p>0.05$) were noted in the control eyes in both maximal sensitivity (-0.8 dB [1.5]) and mean sensitivity (-1.6 dB [0.9]). One patient in whom the vector was not administered to the fovea re-established variable eccentric fixation that included the ectopic island of surviving retinal pigment epithelium that had been exposed to vector.

INTERPRETATION: The initial results of this retinal gene therapy trial are consistent with improved rod and cone function that overcome any negative effects of retinal detachment. These findings lend support to further assessment of gene therapy in the treatment of choroideremia and other diseases, such as age-related macular degeneration, for which intervention should ideally be applied before the onset of retinal thinning.

PMID: 24439297 [PubMed - as supplied by publisher]

Proteomics. 2014 Jan 22. doi: 10.1002/pmic.201300406. [Epub ahead of print]

The utilization of fluorescence to identify the components of lipofuscin by imaging mass spectrometry.

Ablonczy Z, Smith N, Anderson DM, Grey AC, Spraggins J, Koutalos Y, Schey KL, Crouch RK.

Abstract: Lipofuscin, an aging marker in the retinal pigment epithelium (RPE) associated with the development of age-related macular degeneration, is primarily characterized by its fluorescence. The most abundant component of RPE lipofuscin is N-retinylidene-N-retinylethanolamine (A2E) but its exact composition is not known due to the complexity of the RPE extract. In this study, we utilized MALDI imaging to find potential molecules responsible for lipofuscin fluorescence in RPE tissue from Abca4^{-/-}, Sv129, and C57Bl6/J mice ages 2 and 6 month. To assert relationships, the individual images in the MALDI imaging datasets were correlated with lipofuscin fluorescence recorded from the same tissues following proper registration. Spatial correlation information, which is usually is lost in bioanalytics, pinpointed a relatively small number of potential lipofuscin components. The comparison of four samples in each condition further limited the possibility of false positives and provided various new, age- and strain-specific targets. Validating the usefulness of the fluorescence-enhanced imaging strategy, many known adducts of A2E were identified in the short list of lipofuscin components. These results provided evidence that mass spectrometric imaging can be utilized as a tool to begin to identify the molecular substructure of clinically-relevant diagnostic information. This article is protected by copyright. All rights reserved.

PMID: 24453194 [PubMed - as supplied by publisher]

Ophthalmologe. 2014 Jan;111(1):79-92. doi: 10.1007/s00347-013-3005-9.

[Differential diagnosis and therapy of pigment epithelial detachment].[Article in German]

Gamulescu MA, Helbig H, Wachtlin J.

Abstract: Retinal pigment epithelial detachment (PED) can occur associated with multiple ocular and infrequently also primarily non-ocular pathologies. They can be sub-divided into drusenoid, serous, serous-vascularized and fibrovascular PED. Most commonly PED is found in age-related macular degeneration. The knowledge of possible differential diagnoses is important for the prognosis and helps in the choice of therapy and in the individual counseling of patients.

PMID: 24448816 [PubMed - in process]

Pathogenesis

Invest Ophthalmol Vis Sci. 2014 Jan 23. pii: iovs.13-13239v1. doi: 10.1167/iov.13-13239. [Epub ahead of print]

Age-related changes of cystatin C expression and polarized secretion by retinal pigment epithelium: potential age-related macular degeneration links.

Kay P, Yang YC, Hiscott P, Gray D, Maminishkis A, Paraoan L.

Purpose: Cystatin C, a potent cysteine proteinase inhibitor, is abundantly secreted by the retinal pigment epithelium (RPE) and may contribute to regulating protein turnover in the Bruch's membrane (BrM). A variant associated with increased risk of developing age-related macular degeneration (AMD) and Alzheimer's Disease (AD) presents reduced secretion levels from RPE. The purpose of this study was to analyze the effects of age and the accumulation of advanced glycation end-products (AGEs) on the expression and secretion of cystatin C by the RPE.

Methods: Confluent monolayers of human fetal RPE (hFRPE) cells were cultured using an in vitro model mimicking extracellular AGE accumulation. Cystatin C expression, secretion and its polarity were analyzed following culture on AGE-containing BrM mimics (AGED vs non-AGED). Monolayer barrier properties were assessed by transepithelial resistance measurements. The relative level of cystatin C protein expression in human RPE in situ was assessed immunohistochemically in relation to age.

Results: AGE-exposed RPE monolayers presented significantly decreased cystatin C expression and secretion. Basolateral secretion was fully established by week 8 in non-AGED conditions. In AGEd cultures, polarity of secretion was impaired despite maintenance of physiological barrier properties of the monolayer. In the macula region of RPE/choroid segments from human eyes, the level of cystatin C protein was reduced with increasing donor age.

Conclusions: Exposure to AGEs reduces expression of cystatin C and affects its normal secretion in cultured RPE. Age-related changes of cystatin C in the RPE from the posterior pole may compromise its extracellular functions, potentially contributing to AMD pathogenesis.

PMID: 24458156 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Jan 23. pii: iovs.13-13522v1. doi: 10.1167/iov.13-13522. [Epub ahead of print]

Vascular associations and dynamic process motility in perivascular myeloid cells of the mouse choroid: implications for function and senescent change.

Kumar A, Zhao L, McMenamin PG, Fariss R, Wong WT.

Purpose: Immune and vascular alterations in the choroid are implicated in age-related macular degeneration (AMD). As choroidal immune cells are incompletely understood with regards to their physiology and their interactions with choroidal vessels, we examined the associations between myeloid and vascular components of the choroid in young and aged mice.

Methods: Albino CX3CR1GFP/+ transgenic mice, whose choroidal myeloid cells possess green fluorescence, were perfused intraluminally with the vital dye DiI to label choroidal vessels. The distribution, morphology, behavior, and vascular associations of resident myeloid cells were examined using time-lapse live confocal imaging and immunohistochemical analysis.

Results: Dendritiform myeloid cells, the majority resident immune cell population in the choroid, were widely distributed across the choroid and demonstrated close associations with choroidal vessels that vary with their position in the vascular tree. Notably, myeloid cells associated with choroidal arteries and arterioles appeared as elongated cells flanking the long axes of vessels, while those associated with the choriocapillaris were distributed as a layer of stellate cells on the scleral, but not the vitreal, choriocapillaris surface. While stationary in position, dendritiform myeloid cells demonstrated rapid process dynamism well-suited to comprehensive immunosurveillance of the perivascular space. Myeloid cells also increased in density as a function of aging, correlating locally with greater choroidal vascular attenuation.

Conclusions: Resident myeloid cells demonstrated close but dynamic physical interactions with choroidal vessels, indicative of constitutive immune-vascular interactions in the normal choroid. These interactions may alter progressively with aging, providing a basis for understanding age-related choroidal dysfunction underlying AMD.

PMID: 24458147 [PubMed - as supplied by publisher]

J Biol Chem. 2014 Jan 20. [Epub ahead of print]

Fibulin 2, a tyrosine o-sulfated protein, is up-regulated following retinal detachment.

Kanan Y, Brobst D, Westmuckett AD, Moore KL, Han Z, Naash MI, Al-Ubaidi MR.

Abstract: Retinal detachment is the physical separation of the retina from the retinal pigment epithelium. It occurs during aging, trauma or during a variety of retinal disorders such as age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity or as complication following cataract surgery.

This report investigates the role of fibulin 2, an extracellular component, in retinal detachment. A major mechanism for detachment resolution is enhancement of cellular adhesion between the retina and the retinal pigment epithelium and prevention of its cellular migration. This report shows that fibulin 2 is mainly present in the RPE, Bruchs membrane, choriocapillary, and to a lesser degree in retina. In vitro studies revealed the presence of two isoforms for fibulin 2. The small isoform located inside the cell while the large isoform present inside and outside the cells. Furthermore, fibulin 2 is post-translationally modified by tyrosine sulfation and the sulfated isoform is present outside the cell while the unsulfated pool is internally located. Interestingly, sulfated fibulin 2 significantly reduced the rate of cellular growth and migration. Finally, levels of fibulin 2 dramatically increased in the retinal pigment epithelium following retinal detachment, suggesting a direct role for fibulin 2 in the re-attachment of the retina to the retinal pigment epithelium. Understanding the role of fibulin 2 in enhancing retinal attachment is likely to help improve the current therapies or allow the development of new strategies for the treatment of this sight-threatening condition.

PMID: 24446435 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2014 Feb;92(1):27-33. doi: 10.1111/aos.12294. Epub 2013 Nov 6.

Retinal oxygen metabolism in exudative age-related macular degeneration.

Geirsdottir A, Hardarson SH, Olafsdottir OB, Stefánsson E.

PURPOSE: To determine whether retinal vessel oxygen saturation in patients with exudative age-related macular degeneration (AMD) is different from that of a healthy population.

METHODS: Oxygen saturation was measured in retinal arterioles and venules in 46 eyes of 46 treatment-naïve exudative AMD patients and 120 eyes of 120 healthy controls. Simple and multiple linear regression analyses were used to compare the two study groups.

RESULTS: Oxygen saturation in retinal venules increases with age in patients with exudative AMD ($0.45 \pm 0.19\%$ per year; $p = 0.026$), while it decreases with age in healthy individuals ($-0.13 \pm 0.03\%$ per year; $p = 0.0002$). The slopes are statistically different (ANCOVA; $p = 0.0003$). The reverse is true for the arteriovenous difference in oxygen saturation, which decreases with age in AMD patients ($-0.29 \pm 0.16\%$ per year; $p = 0.065$) and increases in healthy individuals ($0.12 \pm 0.03\%$ per year; $p < 0.0001$). At age 80 years, AMD patients have 2.7 percentage points higher venous oxygen saturation than healthy persons and 4.2 percentage points less arteriovenous difference.

CONCLUSIONS: The data suggest that retinal oxygen metabolism may be altered in exudative AMD. The arteriovenous difference is smaller in exudative AMD than in a healthy cohort, consistent with reduced oxygen extraction by retinal vessels in AMD patients. Further studies are needed to fully understand the role of retinal oxygen metabolism in the pathophysiology of exudative AMD.

PMID: 24447786 [PubMed - in process]

Free Radic Biol Med. 2014 Jan 16. pii: S0891-5849(14)00028-8. doi: 10.1016/j.freeradbiomed.2014.01.015. [Epub ahead of print]

Nrf2 Signaling Modulates Cigarette Smoke Induced Complement Activation in Retinal Pigmented Epithelial Cells.

Wang L1, Kondo N2, Cano M3, Ebrahimi K4, Yoshida T5, Barnett BP6, Biswal S7, Handa JT8.

Abstract: While cigarette smoking (CS) and dysregulated complement are thought to play a central role in age-related macular degeneration (AMD), their exact roles are unknown. The aim of this study is to

determine if CS activates complement and if the antioxidant transcription factor Nrf2 modulates this response. In AMD specimens, Nrf2 immunolabeling was strong in the cytoplasm with scattered nuclear labeling of macular retinal pigmented epithelial (RPE) cells that appeared normal, but was decreased and without nuclear labeling in dysmorphic cells overlying drusen, a hallmark AMD lesion. Cigarette smoke extract (CSE) induced Nrf2 nuclear translocation in RPE cells with increased antioxidant and complement gene expression. While CFH protein was not altered by CSE, cell membrane regulator proteins CD46, CD55, and CD59 were decreased, while C3a and C3b, but not iC3b, were increased compared to controls. C5b-9 was increased by CSE, but at sublytic levels only after addition of normal human serum. Nrf2-knockdown enhanced the increase of C3a and C3b from CSE, but not iC3b, C5a, or C5b-9. CSE also increased IL-1b expression and secretion after C3a generation, and was reduced by a C3aR antagonist. In contrast, the Nrf2 activator CDDO-lm restored complement gene expression in RPE cells exposed to CSE. We provide evidence of altered Nrf2 in human AMD, and that CSE induces a pro-inflammatory environment specifically by generating C3a and C3b, and Nrf2 deficiency magnifies this specific complement response.

PMID: 24440594 [PubMed - as supplied by publisher]

Epidemiology

JAMA Ophthalmol. 2014 Jan 23. doi: 10.1001/jamaophthalmol.2013.7682. [Epub ahead of print]

Eye Care Availability and Access Among Individuals With Diabetes, Diabetic Retinopathy, or Age-Related Macular Degeneration.

Gibson DM.

IMPORTANCE: Understanding whether differences in the local availability of eye care professionals are related to differences in realized access to eye care is important for assessing whether and where public health efforts are needed to increase access to eye care professionals.

OBJECTIVE: To examine whether the county-level availability of ophthalmologists and optometrists is associated with measures of realized access to eye care for individuals with diabetes mellitus, diabetic retinopathy, or age-related macular degeneration (ARMD).

DESIGN, SETTING, AND PARTICIPANTS: We studied a cross-sectional sample of US adults 40 years and older (1098 individuals with diabetes, 345 with diabetic retinopathy, and 498 with ARMD) from the 2005-2008 National Health and Nutrition Examination Survey.

MAIN OUTCOMES AND MEASURES: Outcomes were whether diabetic individuals reported undergoing a dilated eye examination in the past year, whether individuals were unaware they had diabetic retinopathy, whether diabetic individuals had vision-threatening diabetic retinopathy, and whether individuals were unaware they had ARMD.

RESULTS: In logistic regression models that also included individual characteristics, individuals who lived in a county in the highest ophthalmologist availability quartile were less likely to be unaware they had diabetic retinopathy (predictive margin [PM], 66.1%; 90% CI, 48.8%-83.4%; vs PM, 84.1%; 90% CI, 78.7%-89.6%) and were less likely to have vision-threatening diabetic retinopathy (PM, 1.4%; 90% CI, 0.9%-1.9%; vs PM, 2.6%; 90% CI, 1.8%-3.4%) than individuals who lived in a county in the lower 3 ophthalmologist availability quartiles. Individuals who lived in a county in the lowest ophthalmologist availability quartile were more likely to be unaware they had ARMD (PM, 93.8%; 90% CI, 90.6%-97.0%; vs PM, 88.3%; 90% CI, 84.7%-91.9%) than individuals who lived a county in the higher 3 ophthalmologist availability quartiles. Optometrist availability quartiles were not significantly related to any of the outcomes.

CONCLUSIONS AND RELEVANCE: The results suggest that efforts to increase access to ophthalmologists to improve outcomes related to diabetic retinopathy or to increase awareness of ARMD should focus on improving access for diabetic individuals who live in counties in the lowest 3 quartiles of

ophthalmologist availability and on individuals at risk of ARMD who live in counties in the lowest quartile of ophthalmologist availability.

PMID: 24458097 [PubMed - as supplied by publisher]

Genetics

Neurobiol Aging. 2013 Dec 19. pii: S0197-4580(13)00646-5. doi: 10.1016/j.neurobiolaging.2013.12.007. [Epub ahead of print]

A search for age-related macular degeneration risk variants in Alzheimer disease genes and pathways.

Logue MW1, Schu M2, Vardarajan BN2, Farrell J2, Lunetta KL3, Jun G4, Baldwin CT2, Deangelis MM5, Farrer LA6.

Abstract: Several lines of inquiry point to overlapping molecular mechanisms between late-onset Alzheimer disease (AD) and age-related macular degeneration (AMD). We evaluated summarized results from large genome-wide association studies for AD and AMD to test the hypothesis that AD susceptibility loci are also associated with AMD. We observed association of both disorders with genes in a region of chromosome 7, including PILRA and ZCWPW1 (peak AMD SNP rs7792525, minor allele frequency [MAF] = 19%, odds ratio [OR] = 1.14, $p = 2.34 \times 10^{-6}$), and with ABCA7 (peak AMD SNP rs3752228, MAF = 0.054, OR = 1.22, $p = 0.00012$). Next, we evaluated association of AMD with genes in AD-related pathways identified by canonical pathway analysis of AD-associated genes. Significant associations were observed with multiple previously identified AMD risk loci and 2 novel genes: HGS (peak SNP rs8070488, MAF = 0.23, OR = 0.91, $p = 7.52 \times 10^{-5}$), which plays a role in the clathrin-mediated endocytosis signaling pathway, and TNF (peak SNP rs2071590, MAF = 0.34, OR = 0.89, $p = 1.17 \times 10^{-5}$), which is a member of the atherosclerosis signaling and the LXR/RXR activation pathways. Our results suggest that AMD and AD share genetic mechanisms.

PMID: 24439028 [PubMed - as supplied by publisher]

Gene. 2014 Jan 16. pii: S0378-1119(14)00053-5. doi: 10.1016/j.gene.2014.01.032. [Epub ahead of print]

Association between complement factor H Val62Ile polymorphism and age-related macular degeneration susceptibility: A meta-analysis.

Wang X1, Geng P2, Zhang Y1, Zhang M3.

BACKGROUND: An increasing body of studies have assessed the contribution of Val62Ile polymorphism to age-related macular degeneration (AMD) risk, but the exact association still remains uncertain. This meta-analysis was undertaken in order to further characterize the potential association between Val62Ile polymorphism and AMD risk in four different ethnic populations.

METHODS: A meta-analysis was performed using data available from 16 case-control studies evaluating correlation between the Val62Ile polymorphism and AMD in Caucasian, Chinese, Japanese and South Korea populations. Data extraction and study quality assessment were performed in duplicate. Summary odds ratios (ORs) and 95% confidence intervals (CIs) of allele contrast and genotype contrast were estimated using the random-effects model. The Q-statistic test was used to identify heterogeneity, and the funnel plot was adopted to evaluate publication bias.

RESULTS: Sixteen studies involving a total of 11,400 subjects based on the search criteria were included in the meta-analysis. In overall populations, the Val62Ile polymorphism seemed to be associated with AMD

(ORAA vs. GG=0.40, 95% CI=0.28-0.59; ORAA+GA vs. GG=0.72, 95% CI=0.64-0.80; ORAA vs. GC+GG=0.50, 95% CI=0.36-0.70; ORA vs. G=0.68, 95% CI=0.58-0.78; ORGA vs. GG=0.71, 95% CI=0.65-0.77). Similarly, subgroup analysis also revealed this polymorphism was related to AMD in all ethnicities.

CONCLUSIONS: This meta-analysis suggested that Val62Ile polymorphism was associated with the susceptibility to AMD.

PMID: 24440287 [PubMed - as supplied by publisher]

Biomed Res Int. 2013;2013:523415. doi: 10.1155/2013/523415. Epub 2013 Dec 18.

Identification of age-related macular degeneration related genes by applying shortest path algorithm in protein-protein interaction network.

Zhang J1, Jiang M2, Yuan F2, Feng KY3, Cai YD4, Xu X1, Chen L5.

Abstract: This study attempted to find novel age-related macular degeneration (AMD) related genes based on 36 known AMD genes. The well-known shortest path algorithm, Dijkstra's algorithm, was applied to find the shortest path connecting each pair of known AMD related genes in protein-protein interaction (PPI) network. The genes occurring in any shortest path were considered as candidate AMD related genes. As a result, 125 novel AMD genes were predicted. The further analysis based on betweenness and permutation test indicates that there are 10 genes involved in the formation or development of AMD and may be the actual AMD related genes with high probability. We hope that this contribution would promote the study of age-related macular degeneration and discovery of novel effective treatments.

PMID: 24455700 [PubMed - in process]

Mol Vis. 2014 Jan 14;20:105-16. eCollection 2014.

CFH haplotypes and ARMS2, C2, C3, and CFB alleles show association with susceptibility to age-related macular degeneration in Mexicans.

Contreras AV1, Zenteno JC2, Fernández-López JC1, Rodríguez-Corona U1, Falfán-Valencia R3, Sebastian L1, Morales F1, Ochoa-Contreras D4, Carnevale A1, Silva-Zolezzi I5.

PURPOSE: To evaluate the contribution of genetic variants of complement factor H (CFH), complement component 2 and 3 (C2 and C3), complement factor B (CFB), and age-related maculopathy susceptibility 2 (ARMS2) to age-related macular degeneration (AMD) risk in the Mexican Mestizo population.

METHODS: Analysis included 282 unrelated Mexican patients with advanced AMD, 205 healthy controls, and 280 population controls. Stereoscopic fundus images were graded on the Clinical Age-Related Maculopathy System (CARMS). We designed a resequencing strategy using primers with M13 adaptor for the 23 exons of the CFH gene in a subgroup of 96 individuals clinically evaluated: 48 AMD cases and 48 age- and sex-matched healthy controls. Single nucleotide polymorphisms (SNPs) in C3 (Arg80Gly and Pro292Leu), C2 (rs547154), CFB (Leu9His), and ARMS2 (Ala69Ser) were genotyped in all patients, healthy and population controls using TaqMan assay.

RESULTS: All evaluated individuals were Mexican Mestizos, and their genetic ancestry was validated using 224 ancestry informative markers and calculating Fst values. The CFH resequencing revealed 19 SNPs and a common variant in the intron 2 splice acceptor site; three CFH haplotypes inferred from individual genotypes, showed significant differences between cases and controls. The risk alleles in C3 (rs1047286, odds ratio [OR]=2.48, 95% confidence interval [CI]=1.64-3.75, p=1.59E-05; rs2230199, OR=2.15, 95% CI=1.48-3.13, p=6.28E-05) and in ARMS2 (rs10490924, OR=3.09, 95% CI=2.48-3.86, p=5.42E-23) were strongly associated with risk of AMD. The protective effect of alleles in C2 (rs547154) and CFB (rs4151667)

showed a trend but was not significantly associated after correction for multiple testing.

CONCLUSIONS: Our results show that ARMS2 and C3 are major contributors to advanced AMD in Mexican patients, while the contributions of CFH, C2, and CFB are minor to those of other populations, revealing significant ethnic differences in minor allele frequencies. We provide evidence that two specific common haplotypes in the CFH gene predispose individuals to AMD, while another may confer reduced risk of disease in this admixed population.

PMID: 24453474 [PubMed - in process]

Diet & lifestyle

Cesk Slov Oftalmol. 2013 Aug;69(3):128-32.

[The Potential use of Honey in Ophthalmology].[Article in Czech]

Majtánová N, Cernák M, Nekorancová J, Cernák A, Majtán J.

Abstract: Honey is considered to be a natural product with antibacterial and anti-inflammatory properties. Its successful application in the treatment of chronic wounds and burns has promoted its further clinical use in other clinical departments, including ophthalmology. One of the major advantages of honey is its multifactorial antibacterial action and the fact that there is no risk of developing bacterial resistance to it. In this work we discuss the current knowledge and new perspectives for honey therapy in treatment of eye diseases such as dry eye disease, age-related macular degeneration, cataracts and bullous keratopathy.

PMID: 24437960 [PubMed - in process]

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