

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

BMJ Clin Evid. 2016 Feb 24;2016.

Age-related macular degeneration: anti-vascular endothelial growth factor treatment.

Arnold JJ.

INTRODUCTION: Sight-threatening (late) age-related macular degeneration (AMD) is found in about 1.4% of people of European ancestry aged 70 years, with prevalence increasing with age. Early-stage disease is marked by normal vision but retinal changes (drusen and pigment changes). Disease progression leads to worsening central vision, but peripheral vision is generally preserved.

METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of treatments for exudative age-related macular degeneration? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2014 (Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview).

RESULTS: At this update, searching of electronic databases retrieved 901 studies. After deduplication and removal of conference abstracts, 597 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 423 studies and the further review of 174 full publications. Of the 174 full articles evaluated, two systematic reviews, 10 RCTs, and four further reports were added at this update. We performed a GRADE evaluation of the quality of evidence for nine PICO combinations.

CONCLUSIONS: In this systematic overview, we categorised the efficacy for four interventions, based on information relating to the effectiveness and safety of anti-angiogenesis (using aflibercept, bevacizumab, and ranibizumab) and ranibizumab plus photodynamic therapy with verteporfin.

PMID: 26909890 [PubMed - in process]

Immunotherapy. 2016 Feb 24. [Epub ahead of print]

Aflibercept for the treatment of diabetic macular edema.

Harkins KA, Haschke M, Do DV.

Abstract: Diabetic macular edema (DME) is an accumulation of fluid in the central retina, secondary to vascular-leakage from diabetic vascular damage. DME and other ophthalmic sequela of diabetes are the leading cause of blindness in 20 to 74-year-olds. The development of VEGF-inhibitors (anti-VEGF) has revolutionized DME treatment improving the clinician's ability to remove excess fluid from the macula, improving visual-acuity. Aflibercept is an anti-VEGF agent made of a recombinant fusion protein (consisting of VEGF receptors 1 and 2 extracellular domains) fused with the Fc-portion of human-IgG1, which binds both VEGF isoforms A and B, and placental growth factor. Phase III clinical trials and published scientific

studies have demonstrated the efficacy of intravitreal aflibercept injection in the treatment of DME.

PMID: 26907516 [PubMed - as supplied by publisher]

Ophthalmology. 2016 Feb 20. [Epub ahead of print]

Single-Chain Antibody Fragment VEGF Inhibitor RTH258 for Neovascular Age-Related Macular Degeneration: A Randomized Controlled Study.

Holz FG, Dugel PU, Weissgerber G, Hamilton R, Silva R, Bandello F, Larsen M, Weichselberger A, Wenzel A, Schmidt A, Escher D, Sararols L, Souied E.

PURPOSE: To assess the safety and efficacy of different doses of RTH258 applied as single intravitreal administration compared with ranibizumab 0.5 mg in patients with neovascular age-related macular degeneration (AMD).

DESIGN: Six-month, phase 1/2, prospective, multicenter, double-masked, randomized, ascending single-dose, active-controlled, parallel-group study.

PARTICIPANTS: A total of 194 treatment-naïve patients, aged ≥ 50 years, with primary subfoveal choroidal neovascularization secondary to AMD.

METHODS: Patients received a single intravitreal injection of RTH258 0.5 mg ($n = 11$), 3.0 mg ($n = 31$), 4.5 mg ($n = 47$), or 6.0 mg ($n = 44$), or ranibizumab 0.5 mg ($n = 61$).

MAIN OUTCOME MEASURES: The primary efficacy end point was the change from baseline to month 1 in central subfield thickness (CSFT) measured by spectral-domain optical coherence tomography. The secondary efficacy end point was the duration of treatment effect measured as time from the initial injection to receipt of post-baseline therapy (PBT) guided by protocol-defined criteria. Adverse events (AEs) were recorded throughout the study.

RESULTS: RTH258 demonstrated noninferiority compared with ranibizumab in mean change in CSFT from baseline to month 1 for the 4.5- and 6.0-mg dose groups (margin: 40 μm , 1-sided $\alpha 0.05$). The difference in CSFT change at month 1 comparison with ranibizumab was 22.86 μm (90% confidence interval [CI], -9.28 to 54.99) and 19.40 μm (95% CI, -9.00 to 47.80) for RTH258 4.5 and 6 mg, respectively. The median time to PBT after baseline therapy was 60 and 75 days for patients in the RTH258 4.5- and 6.0-mg groups, respectively, compared with 45 days for ranibizumab. Changes in best-corrected visual acuity with RTH258 were comparable to those observed with ranibizumab. The most frequent AEs reported for the RTH258 groups were conjunctival hemorrhage, eye pain, and conjunctival hyperemia; the majority of these events were mild in intensity.

CONCLUSIONS: This first-in-human study of RTH258 demonstrated noninferiority in the change in CSFT at 1 month for the 4.5- and 6.0-mg doses compared with ranibizumab and an increase of 30 days in the median time to PBT for the 6.0-mg dose. There were no unexpected safety concerns, and the results support the continued development of RTH258 for the treatment of neovascular AMD.

PMID: 26906165 [PubMed - as supplied by publisher]

Eye (Lond). 2016 Feb 26. [Epub ahead of print]

Determining patient preferences in the management of neovascular age-related macular degeneration: a conjoint analysis.

Baxter JM, Fotheringham AJ, Foss AJ.

Purpose: To determine the opinions from a patient perspective on relevant variables in the delivery of treatment for neovascular age-related macular degeneration (nAMD).

Methods: Pilot interviews with patients and doctors were conducted to identify what variables in the provision of a nAMD service were important. This led to the generation of two sets of scenario options. Subsequently 100 patients undergoing active treatment for nAMD in the National Health Service University Hospital, United Kingdom underwent interview assessment. They were asked to rank their preferences for provision of their care with reference to these two sets of scenario options. Using conjoint analysis, percentage preferences, and utility scores for each variable in each scenario design were calculated.

Results: Ninety-five patients completed the preference ranking for both scenarios. Eight patients ranked worse vision as preferable to better vision and were excluded on the basis that they had not understood the task. The results of the remaining 87 patients are presented. The most important factor to patients was having good vision, followed by a one-stop service and less frequent follow up. The least important factors were label status of the drug, cost to the health service, and grade of the injector.

Conclusion: Patients regard good vision and minimal visits to the hospital above the status of injector, label status of drug, or cost to the NHS. Eye advance online publication, 26 February 2016; doi:10.1038/eye.2016.18.

PMID: 26915744 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2016 Feb 15. [Epub ahead of print]

Anti-VEGF and its impact on the outer retina: retinal pigment epithelium tear after an injection of aflibercept in contralateral eye. [Article in English, Spanish]

Campos Polo R, Rubio Sánchez C.

CASE REPORT: A 62-year-old woman with a history of bilateral retinal pigment epithelium detachment (PED), secondary of age-related macular degeneration (AMD), who presented with a retinal pigment epithelium (RPE) tear on her left eye after an aflibercept injection in the contralateral eye one month earlier.

DISCUSSION: A RPE tear is the main complication when the anti-VEGF therapy is used for the management of the PED. Furthermore, it should be noted that systemic absorption of the drug can induce an effect on the untreated eye.

PMID: 26899882 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2016 Feb 25. [Epub ahead of print]

Topical Dorzolamide-Timolol With Intravitreal Anti-Vascular Endothelial Growth Factor for Neovascular Age-Related Macular Degeneration.

Sridhar J, Hsu J, Shahlaee A, Garg SJ, Sporn MJ, Fineman MS, Vander J.

IMPORTANCE: There is a subset of eyes with neovascular age-related macular degeneration (AMD) that have persistent exudation despite fixed-interval intravitreal anti-vascular endothelial growth factor (VEGF) injections.

OBJECTIVE: To evaluate the effect of topical dorzolamide hydrochloride-timolol maleate on anatomic and functional outcomes in eyes with neovascular AMD and incomplete response to anti-VEGF therapy.

DESIGN, SETTING, AND PARTICIPANTS: An exploratory, prospective single-arm interventional study at a tertiary referral academic private practice. Patients with neovascular AMD and persistent macular edema despite fixed-interval intravitreal anti-VEGF therapy were enrolled. Baseline spectral-domain optical coherence tomography and clinical data, including visual acuity and intraocular pressure, were obtained at enrollment and from one visit before enrollment. The study was performed at the Retina Service of Wills Eye Hospital and the offices of Mid Atlantic Retina from February 1, 2015, through September 30, 2015.

Patients were followed up for at least 2 visits after enrollment. Central subfield thickness, maximum subretinal fluid height, and maximum pigment epithelial detachment height from spectral-domain optical coherence tomography were recorded at each visit.

INTERVENTIONS: Enrolled eyes received a regimen of topical dorzolamide-timolol twice daily and continued to receive the same intravitreal anti-VEGF therapy at the same interval as received before enrollment for the duration of the study.

MAIN OUTCOMES AND MEASURES: Change in central subfield thickness was the primary outcome measure. Changes in maximum subretinal fluid height, maximum pigment epithelial detachment height, and visual acuity were the secondary outcome measures.

RESULTS: Ten patients (10 eyes) completed the study. The mean age of the patients was 78.2 years (age range, 65-91 years), and 6 were male. Eight eyes received intravitreal aflibercept, and 2 eyes received intravitreal ranibizumab. All study eyes had been receiving long-term anti-VEGF therapy with the same medication before study enrollment for a mean of 21.9 injections. The mean central subfield thickness decreased from 419.7 μm at enrollment to 334.1 μm at the final visit ($P = .01$). The mean maximum subretinal fluid height decreased from 126.6 μm at enrollment to 49.5 μm at the final visit ($P = .02$). The mean maximum pigment epithelial detachment height decreased from 277.4 μm at enrollment to 239.9 μm at the final visit ($P = .12$). The mean logMAR visual acuity were 0.54 at enrollment and 0.48 at the final visit ($P = .60$).

CONCLUSIONS AND RELEVANCE: These data suggest that topical dorzolamide-timolol may reduce central subfield thickness and subretinal fluid in eyes with persistent exudation despite consistent, fixed-interval intravitreal anti-VEGF treatment for neovascular AMD.

PMID: 26914218 [PubMed - as supplied by publisher]

Cutan Ocul Toxicol. 2016 Feb 24;1-4. [Epub ahead of print]

The effect and safety of intravitreal injection of ranibizumab and bevacizumab on the corneal endothelium in the treatment of diabetic macular edema.

Guzel H, Bakbak B, Koylu MT, Gonul S, Ozturk B, Gedik S.

OBJECTIVE: To investigate the effect and safety of intravitreal injection (IVI) of bevacizumab and ranibizumab on corneal endothelial cell count and morphology in patients with diabetic macular edema.

MATERIALS AND METHODS: A total of 60 eyes from 60 consecutive patients who received 0.5 mg/0.05 ml IVIs of bevacizumab ($n = 30$, IVB group) or 1.25 mg/0.05 ml ranibizumab ($n = 30$, IVR group) for three consecutive months were investigated prospectively. Specular microscopy was performed to evaluate endothelial cell count, the percentage of hexagonal cells (pleomorphism), and the coefficient of variation of the cell size (polymegathism); optical biometry was performed to evaluate central corneal thickness. Results before injection and 1 month after the first and third injections were compared.

RESULTS: The groups were matched for age ($p = 0.11$) and gender ($p = 0.32$). There was no significant difference in endothelial cell count (IVB group, $p = 0.66$; IVR group, $p = 0.74$), pleomorphism (IVB group, $p = 0.44$; IVR group, $p = 0.88$) and polymegathism (IVB group, $p = 0.21$; IVR group, $p = 0.24$) before injection or 1 month after the first and third injections. There was also no difference in central corneal thickness (IVB group, $p = 0.15$; IVR group, $p = 0.58$) before injection or 1 month after the first and third injections.

CONCLUSION: Monthly 1.25 mg/0.05 ml IVIs of bevacizumab or 0.5 mg/0.05 ml of ranibizumab for three consecutive months in the treatment of diabetic macular edema does not affect corneal morphology and has no harmful effects on the endothelium.

PMID: 26911396 [PubMed - as supplied by publisher]

Curr Opin Ophthalmol. 2016 Feb 24. [Epub ahead of print]

Recent advancements in diabetic retinopathy treatment from the Diabetic Retinopathy Clinical Research Network.

Baker CW, Jiang Y, Stone T.

PURPOSE OF REVIEW: Diabetic retinopathy and diabetic macular edema (DME) are common eye diseases leading to vision loss. The Diabetic Retinopathy Clinical Research Network (DRCRnet), a collaboration of private and academic practices supported by the National Eye Institute and the National Institute of Diabetes, Digestive and Kidney Diseases has studied diabetic eye disease for 13 years. This review will discuss the network's findings over the last year, when some of its most important contributions were reported.

RECENT FINDINGS: The DRCRnet reported intravitreal bevacizumab, ranibizumab and aflibercept all improve visual acuity in DME. With baseline vision of 20/30 to 20/40, all agents had similar efficacy. With baseline vision of 20/50 or worse, aflibercept resulted in superior visual improvement. Protocol S, which compared panretinal photocoagulation with intravitreal injections of ranibizumab for proliferative diabetic retinopathy (PDR), found vision outcomes and surgery rates were not inferior in the injection group. Secondary outcomes indicate improved functional results with ranibizumab supporting injections as a possible alternative treatment for PDR.

SUMMARY: The DRCRnet has helped clarify the role of various treatments for both DME and PDR, and will continue to evaluate treatments for these vision-threatening conditions.

PMID: 26913740 [PubMed - as supplied by publisher]

Jpn J Ophthalmol. 2016 Feb 26. [Epub ahead of print]

Combination therapy with intravitreal tissue plasminogen activator and ranibizumab for subfoveal type 2 choroidal neovascularization.

Kachi I, Yasukawa T, Kato A, Takase N, Morita H, Kubota A, Hirano Y, Uemura A, Ogura Y.

PURPOSE: Fibrovascular scar formation related to subfoveal type 2 choroidal neovascularization (CNV) often causes severe vision loss in eyes with age-related macular degeneration. The authors assessed additional impacts of intravitreal tissue plasminogen activator (tPA), a fibrinolytic compound, combined with intravitreal ranibizumab (IVR) on subfoveal type 2 CNV.

METHODS: Eight eyes of eight patients with type 2 CNV underwent intravitreal injections of ranibizumab and tPA (IVR/tPA) (40 kIU). Twelve eyes of 12 patients with type 2 CNV were treated with only IVR injections, as the control group. For retreatment, IVR was performed as needed. The best-corrected visual acuity (BCVA) and the central retinal thickness (CRT) and macular volume (MV) on optical coherence tomography were recorded periodically for 6 months.

RESULTS: The subretinal fibrinous and fibrovascular tissue complex regressed or contracted immediately after administration of IVR/tPA in contrast to IVR monotherapy. The total numbers of IVR injections did not differ significantly between the two groups. The mean logarithm of the minimum angle of resolution BCVA in the combination therapy group improved significantly from 0.72 at baseline to 0.51 at month 6 and was superior to that in the monotherapy group (0.70-0.79). The improvements of the mean CRT and MV in the combination therapy group were superior to the monotherapy group. No tPA-related complications developed.

CONCLUSIONS: tPA may have a specific ability to regress already formed subretinal fibrinous and fibrovascular tissue complexes in eyes with type 2 CNV, potentially increasing the chances of visual improvement through a synergistic relationship with anti-VEGF therapies.

PMID: 26919844 [PubMed - as supplied by publisher]

Ophthalmologe. 2016 Feb 26. [Epub ahead of print]

[Long-term results in neovascular age-related macular degeneration : Changes in visual acuity and geographic atrophy during long-standing anti-VEGF therapy]. [Article in German]

Thalgott V, Feucht N, Lohmann CP, Maier M.

BACKGROUND: In neovascular age-related macular degeneration (nAMD) intravitreal injection of anti-vascular endothelial growth factor (VEGF) is the standard therapy. According to the results of the CATT study with reference to the potential relationship between ranibizumab injections and the occurrence of geographic atrophy (GA) this retrospective real life evaluation was performed.

MATERIAL AND METHODS: Eyes with more than 28 intravitreal anti-VEGF injections (IVT) using bevacizumab, pegaptanib, ranibizumab or aflibercept were evaluated with respect to visual acuity and geographic atrophy using the RegionFinder of Heidelberg Engineering. For statistical analysis the Wilcoxon rank test was used (SPSS version 20, SPSS, Chicago, IL).

RESULTS: In this study 56 eyes were evaluated with a median number of 41.5 (range 28-66) injections, which corresponds to an injection rate of 6.8 IVT per year. The median visual acuity at baseline was 0.4 logMAR $\pm$ 0.32 (range 0-1.2) and 0.6 logMAR $\pm$ 0.33 (range 0.1-1.7) at the end of the observation period. This decrease was statistically significant ($p = 0.029$). In 55.8 % of the eyes visual acuity was equal or better after a median of 6 years follow-up whereas 23.3 % revealed a visual acuity that was ≤ 0.3 logMAR. Of the eyes 30 % showed a clearly defined GA. The median GA at baseline was 0.45 mm² (range 0-6.24) and at the time of evaluation 4.36 mm² (range 0.95-24.71) corresponding to an annual growth of 0.49 mm²/year.

CONCLUSION: In conjunction with the results of other long-term studies it can be assumed that despite regular monitoring and long-term treatment not all patients with nAMD can be protected against a final loss of visual acuity over the years; however, more than 50 % of the eyes could maintain a stable or improved visual acuity. With respect to GA this small collective showed growth rates that are comparable to those in slowly progressing dry AMD. Thus no evidence was found for accelerated increase of GA during IVT therapy.

PMID: 26920612 [PubMed - as supplied by publisher]

Eye Sci. 2015 Jun;30(2):63-6, 69.

Intravitreal Aflibercept for Macular Edema Secondary to Branch Retinal Vein Occlusion in Chinese Patients.

Wang JK, Huang TL, Su PY, Chang PY, Tseng YY.

PURPOSE: To investigate the short-term efficacy and safety of intravitreal aflibercept in a case series of patients from Taiwan, China, with macular edema secondary to branch retinal vein occlusion (BRVO).

METHODS: A total of 32 patients with macular edema associated with BRVO, without prior macular laser or other intervention, were enrolled consecutively from September 2013 to February 2015. The cases received single 2 mg injections of intravitreal aflibercept. Primary outcome measures included changes in central foveal thickness (CFT; 1 mm increments by spectral-domain optic coherence tomography) and best corrected visual acuity (BCVA), determined at 1, 2, and 3 months after the injection. Complications after injections were recorded. The changes in CFT and BCVA were compared with Wilcoxon sign-rank tests.

RESULTS: The CFT was significantly reduced and the BCVA was significantly improved at 1, 2, and 3 months after injection (all $P < 0.05$). Tomography findings revealed no recurrence within 3 months. No systemic thromboembolic events, elevated intraocular pressure, retinal detachment, or infectious endophthalmitis occurred following injection.

CONCLUSION: Single intravitreal aflibercept may be useful in treating macular edema associated with BRVO within 3 months. No adverse systemic or ocular effects were found in this case series.

PMID: 26902063 [PubMed - in process]

Oman J Ophthalmol. 2015 Sep-Dec;8(3):185-7.

Anti-vascular endothelial growth factors for choroidal neovascularization secondary to choroidal osteoma: Long-term results.

Lekha T, Renuka NS, Prasad HN.

Abstract: Choroidal osteoma is an uncommon benign osseous intraocular tumor typically seen unilaterally in young women. Visual loss can occur due to choroidal neovascularization (CNV) complicating osteoma. We report a rare case of bilateral choroidal osteoma with secondary CNV in a young male and the long-term results following anti-vascular endothelial growth factor (VEGF) therapy. A 30-year-old male with history of defective vision in both eyes since several years and recent worsening in the right eye (RE) since 2 months was found to have bilateral macular osteoma with CNV in the RE based on clinical evaluation, fluorescein angiography, optical coherence tomography, and ultrasonography. Intravitreal injection of ranibizumab at monthly intervals for three doses resulted in resolution of CNV and remained stable for 5 years. Recurrent CNV detected 6 years later responded to an injection of intravitreal bevacizumab and has remained stable till date. Anti-VEGF therapy stabilized the secondary CNV in our patient for 7 years with satisfactory structural and functional outcome, demonstrating the long-term efficacy of this modality of treatment.

PMID: 26903728 [PubMed] PMCID: PMC4738667

Oman J Ophthalmol. 2015 Sep-Dec;8(3):166-70.

Experience of intravitreal injections in a tertiary Hospital in Oman.

Al-Hinai AS.

AIM: To find out statistical data regarding intravitreal injections in an outpatient department setup at a tertiary center in Oman.

DESIGN: Retrospective chart review.

METHODS: Data collection of patients who underwent intravitreal injections from November 2009 to May 2013 at Sultan Qaboos University Hospital.

RESULTS: Throughout a period of 42 months, a total of 711 intravitreal injections were performed. That included 214 patients (275 eyes). Around one-third of the eyes received two injections or more. The injected agents were bevacizumab (59.8%), ranibizumab (32.3%), triamcinolone (7.5%), and very few patients with endophthalmitis received intravitreal antibiotics and antifungal agents. The three most common indications for the injection therapy were diabetic macular edema (50.9%), choroidal neovascularization (24.3%), and retinal vein occlusive diseases (11.5%). Serious adverse events were rare, and they occurred as ocular (0.9% per patient) and systemic (3.3% per patient). There were 42 eyes received intravitreal triamcinolone, and 24% of them developed intraocular hypertension that required only medical treatment.

CONCLUSION: Different intravitreal agents are currently used to treat many ocular diseases. Currently, therapy with intravitreal agents is very popular, and it carries a promising outcome with more efficiency and safety.

PMID: 26903722 [PubMed] PMCID: PMC4738661

Ophthalmology. 2016 Mar;123(3):e21.

Re: Veloso et al.: Vitreomacular interface after anti-vascular endothelial growth factor injections in neovascular age-related macular degeneration (Ophthalmology 2015;122:1569-72).

Khanduja S, Singh S, Kinra V.

PMID: 26902570 [PubMed - in process]

Other treatment & diagnosis

Eye (Lond). 2016 Feb 26. [Epub ahead of print]

Stellate nonhereditary idiopathic foveomacular retinoschisis concomitant to exudative maculopathies.

Casalino G, Upendran M, Bandello F, Chakravarthy U.

Purpose: To report the clinical course of patients presenting with stellate nonhereditary idiopathic foveomacular retinoschisis (SNIFR) concomitant with exudative maculopathies.

Methods: Retrospective case series. Multimodal imaging findings, including spectral-domain optical coherence tomography (SD-OCT) were reviewed. Genetic testing for the RS1 gene was performed in one patient.

Results: We identified two female patients who fit the definition of SNIFR and presented with concomitant neovascular age-related macular degeneration (n-AMD). In both the patients, SD-OCT showed exudative macular features and splitting (bilateral in patient 1, unilateral in patient 2) of the outer plexiform layer (OPL) in the macula with no other evidence of hereditary or an acquired predisposing condition. Genetic testing excluded mutation of RS1 gene in patient 1. The fundi of both the patients showed characteristic signs of active choroidal neovascularization (CNV) and following anti-VEGF treatment, visual acuity improved and CNV-related exudative changes resolved. However, the split along the OPL remained unaltered.

Conclusions: SNIFR may be associated with n-AMD. It is important to recognise the presence of retinoschisis when there is other exudative pathology as the former may be misinterpreted as intraretinal fluid, prompting unnecessary treatment. Eye advance online publication, 26 February 2016; doi:10.1038/eye.2016.17.

PMID: 26915743 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2016 Feb 1;57(2):739-45.

The Association Between Subretinal Drusenoid Deposits in Older Adults in Normal Macular Health and Incident Age-Related Macular Degeneration.

Huisingh C, McGwin G Jr, Neely D, Zarubina A, Clark M, Zhang Y, Curcio CA, Owsley C.

PURPOSE: Subretinal drusenoid deposits (SDD) have been associated with the progression to late age-related macular degeneration (AMD). To determine whether SDD in eyes in normal macular health increases risk for early AMD, this study examined the association between presence of SDD at baseline in a cohort of older adults in normal macular health and incident AMD 3 years later.

METHODS: Subjects enrolled in the Alabama Study on Early Age-Related Macular Degeneration (ALSTAR) were assessed for the presence of SDD using color fundus photos, infrared reflectance and fundus autofluorescence images, and spectral-domain optical coherence tomography volumes. The study sample included 799 eyes from 455 participants in normal macular health per grading of color fundus photographs using the 9-step Age-Related Eye Disease Study (AREDS) classification system. Age-related macular degeneration was defined as eyes having an AREDS grade ≥ 2 at the 3-year follow-up.

RESULTS: Twenty-five percent of participants had SDD in one or both eyes at baseline. At follow-up visit, 11.9% of eyes in the sample developed AMD. Compared to eyes without SDD, those with SDD were 2.24

(95% confidence interval [CI] 1.36-3.70) times more likely to have AMD at follow-up. After adjusting for age, C-reactive protein quartile, and family history of AMD, the association persisted.

CONCLUSIONS: Results suggest that SDD in older eyes with normal macular health as defined by the AREDS scale is a risk factor for the development of early AMD. Older adults in seemingly normal macular health yet having SDD may warrant closer clinical monitoring for the possible onset of early AMD.

PMID: 26906160 [PubMed - in process] PMCID: PMC4771176 [Available on 2016-08-01]

Isr Med Assoc J. 2015 Dec;17(12):750-4.

Lamellar Macular Holes Associated with End-Stage Exudative Age-Related Macular Degeneration.

Segal O, Ferencz JR, Mimouni M, Nesher R, Cohen P, Nemet AY.

BACKGROUND: Reports of lamellar macular holes (LMHs) with underlying age-related macular degeneration (AMD) are rare, and the specific definition, pathogenesis and surgical recommendations for this macular condition remain unclear.

OBJECTIVES: To present a series of LMHs in eyes with underlying end-stage AMD, and describe optical coherence tomography (OCT) detection of associated morphologic abnormalities.

METHODS: We reviewed the files of consecutive patients diagnosed with LMH and underlying end-stage AMD between September 2007 and September 2011.

RESULTS: Sixteen eyes of 14 patients were included in this study. The average follow-up after the OCT-established diagnosis of LMH was 19.8 months (range 4-48). The average visual acuity (VA) at last follow-up visit was 20/400 (20/60-20/1200). The best-corrected VA was stable in 10 eyes (62.5%) and deteriorated in 6 (37.5%). There was a statistically significant correlation between VA and minimal foveal thickness ($r = -0.598$, $P = 0.014$).

CONCLUSIONS: In this series of LMHs with underlying AMD the OCT findings were intraretinal fluid, cystic spaces and window defect.

PMID: 26897976 [PubMed - in process]

Pathogenesis

Exp Eye Res. 2016 Feb 23. [Epub ahead of print]

IBI302, a Promising Candidate for AMD Treatment, Targeting Both the VEGF and Complement System with High Binding Affinity in vitro and Effective Targeting of the Ocular Tissue in Healthy Rhesus Monkeys.

Ren X, Li J, Xu X, Wang C, Cheng Y.

Abstract: Uncontrolled activation of complement and upregulation of vascular endothelial growth factor (VEGF) play fundamental roles in age-related macular degeneration (AMD). However, most drugs used to treat AMD focus on a single target, and the percentage of effectively treated patients in clinical practice needs to be improved. Therefore, novel AMD treatment approaches are needed. IBI302 is a novel bispecific decoy receptor fusion protein designed with both a VEGF inhibition domain and a complement cascade inhibition domain, which are connected by the Fc region of human immunoglobulin. In this study, we systematically evaluated the binding affinity between IBI302 and VEGF isoforms and complement proteins by using surface plasmon resonance (SPR) technology. Anti-VEGF blockers (aflibercept and bevacizumab) and complement receptor 1 were used as references. The SPR assay results indicated that IBI302 could bind different VEGF isoforms and complement proteins with high affinity. The biological

activity of IBI302 was also studied. IBI302 showed an inhibitory effect on human primary umbilical vein endothelial cell proliferation and the activation of complement pathways in vitro. Finally, the pharmacokinetic (PK) properties of IBI302 were evaluated in rhesus monkeys. The PK results showed that after a 0.5 mg/eye intravitreal dosage, IBI302 became rapidly distributed from the vitreous humor into targeted tissues and remained active over 504 h. Overall, the favorable anti-angiogenic and anti-complement effects of IBI302 along with the good PK profiles in rhesus monkeys support the selection and development of IBI302 as a promising candidate for AMD treatment.

PMID: 26919788 [PubMed - as supplied by publisher]

EMBO Mol Med. 2016 Feb 24;8(3):208-31.

Increased VEGF-A promotes multiple distinct aging diseases of the eye through shared pathomechanisms.

Marneros AG

Abstract: While increased VEGF-A has been associated with neovascular age-related macular degeneration (AMD), it is not known whether VEGF-A may also promote other age-related eye diseases. Here, we show that an increase in VEGF-A is sufficient to cause multiple distinct common aging diseases of the eye, including cataracts and both neovascular and non-exudative AMD-like pathologies. In the lens, increased VEGF-A induces age-related opacifications that are associated with ERK hyperactivation, increased oxidative damage, and higher expression of the NLRP3 inflammasome effector cytokine IL-1 β . Similarly, increased VEGF-A induces oxidative stress and IL-1 β expression also in the retinal pigment epithelium (RPE). Targeting NLRP3 inflammasome components or IL1r1 strongly inhibited not only VEGF-A-induced cataract formation, but also both neovascular and non-exudative AMD-like pathologies. Moreover, increased VEGF-A expression specifically in the RPE was sufficient to cause choroidal neovascularization (CNV) as in neovascular AMD, which could be inhibited by RPE-specific inactivation of Flk1, while Tlr2 inactivation strongly reduced CNV. These findings suggest a shared pathogenic role of VEGF-A-induced and NLRP3 inflammasome-mediated IL-1 β activation for multiple distinct ocular aging diseases.

PMID: 26912740 [PubMed - in process] Free full text

J Neural Eng. 2016 Feb 23;13(2):025001. [Epub ahead of print]

Changes in ganglion cell physiology during retinal degeneration influence excitability by prosthetic electrodes.

Cho A, Ratliff C, Sampath A, Weiland J.

OBJECTIVE: Here we investigate ganglion cell physiology in healthy and degenerating retina to test its influence on threshold to electrical stimulation.

APPROACH: Age-related Macular Degeneration and Retinitis Pigmentosa cause blindness via outer retinal degeneration. Inner retinal pathways that transmit visual information to the central brain remain intact, so direct electrical stimulation from prosthetic devices offers the possibility for visual restoration. Since inner retinal physiology changes during degeneration, we characterize physiological properties and responses to electrical stimulation in retinal ganglion cells (RGCs) of both wild type mice and the rd10 mouse model of retinal degeneration.

MAIN RESULTS: Our aggregate results support previous observations that elevated thresholds characterize diseased retinas. However, a physiology-driven classification scheme reveals distinct sub-populations of ganglion cells with thresholds either normal or strongly elevated compared to wild-type. When these populations are combined, only a weakly elevated threshold with large variance is observed. The cells with normal threshold are more depolarized at rest and exhibit periodic oscillations.

SIGNIFICANCE: During degeneration, physiological changes in RGCs affect the threshold stimulation currents required to evoke action potentials.

PMID: 26905177 [PubMed - as supplied by publisher]

Neuroscience. 2016 Feb 21. [Epub ahead of print]

Activation of type 5 metabotropic glutamate receptor promotes the proliferation of rat retinal progenitor cell via activation of the PI-3-K and MAPK signaling pathways.

Zhang Z, Hu F, Liu Y, Ma B, Chen X, Zhu K, Shi Y, Wei T, Xing Y, Gao Y, Lu H, Liu Y, Kang Q.

Abstract: The metabotropic glutamate receptor 5 (mGluR5) regulates neurogenesis in the brain, but the effect of mGluR5 on retinal progenitor cells (RPCs) remains unknown. In this study, we found that mGluR5 promoted the proliferation of rat RPCs with activation of the phosphatidylinositol-3-kinase (PI-3-K) and mitogen-activated protein kinase (MAPK) signaling pathways in vitro. The mGluR5 agonist (S)-3,5-dihydroxyphenylglycine hydrate (DHPG) increased the cellular viability in a concentration- and time-dependent manner, whereas the mGluR5 antagonist 6-methyl-2-(phenylethynyl)pyridine hydrochloride (MTEP) had the opposite effect, as shown by 3-((2-methyl-1,3-thiazol-4-yl)ethynyl)pyridine hydrochloride (MTT) assay. Treatment with DHPG (100 μ M) also promoted the proliferation of RPCs, as indicated by 5-Bromo-2-deoxyUridine (BrdU) staining and flow cytometry, and likewise, MTEP (100 μ M) and mGluR5 knockdown abolished the action of mGluR5 activity. Western blot demonstrated that the activation of mGluR5 enhanced the expression of Cyclin D1 and the phosphorylation level of PKC however, MTEP or mGluR5 knockdown also abrogated the effect of DHPG on RPCs. Furthermore, we found that activation of the extracellular signal-regulated protein kinase (ERK) and protein kinase B (AKT) signaling pathways was involved in the proliferation of RPC. After DHPG treatment, the levels of both p-ERK1/2 and p-AKT increased in a time-dependent manner. Then we used MTEP, mGluR5 knockdown, the ERK1/2 inhibitor U0126 and the AKT inhibitor LY294002 to pretreat the cells, and all of them clearly eliminated the influence of DHPG. These results demonstrated that mGluR5 regulates neurogenesis in RPCs through the MAPK and PI-3-K signaling pathways, and these findings may motivate a pharmacological study investigating a potential mechanism for the treatment of retinal diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD).

PMID: 26902516 [PubMed - as supplied by publisher]

Mol Vis. 2016 Feb 3;22:116-28. eCollection 2016.

TNF- α mediates choroidal neovascularization by upregulating VEGF expression in RPE through ROS-dependent β -catenin activation.

Wang H, Han X, Wittchen ES, Hartnett ME.

PURPOSE: Inflammation, oxidative stress, and angiogenesis have been proposed to interact in age-related macular degeneration. It has been postulated that external stimuli that cause oxidative stress can increase production of vascular endothelial growth factor (VEGF) in retinal pigment epithelial (RPE) cells. In this study, we tested the hypothesis that the inflammatory cytokine, tumor necrosis factor alpha (TNF- α), contributed to choroidal neovascularization (CNV) by upregulating VEGF in RPE through intracellular reactive oxygen species (ROS)-dependent signaling and sought to understand the mechanisms involved.

METHODS: In a murine laser-induced CNV model, 7 days after laser treatment and intravitreal neutralizing mouse TNF- α antibody or isotype immunoglobulin G (IgG) control, the following measurements were made: 1) TNF- α protein and VEGF protein in RPE/choroids with western blot, 2) CNV volume in RPE/choroidal flatmounts, and 3) semiquantification of oxidized phospholipids stained with E06 antibody within CNV with immunohistochemistry (IHC). In cultured human RPE cells treated with TNF- α or PBS control, 1) ROS generation was measured using the 2',7'-dichlorodihydrofluorescein diacetate (DCFDA) fluorescence

assay, and 2) NOX4 protein and VEGF protein or mRNA were measured with western blot or quantitative real-time PCR in cells pretreated with apocynin or nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) inhibitor, VAS 2870, or transfected with p22phox siRNA, and each was compared to its appropriate control. Western blots of phosphorylated p65 (p-p65), total p65 and β -actin, and quantitative real-time PCR of VEGF mRNA were measured in human RPE cells treated with TNF- α and pretreatment with the nuclear factor kappa B inhibitor, Bay 11-7082 or control. Western blots of β -catenin, VEGF, and p22phox and coimmunoprecipitation of β -catenin and T-cell transcriptional factor were performed in human RPE cells treated with TNF- α following pretreatment with β -catenin transcriptional inhibitors, XAV939 or JW67, or transfection with p22phox siRNA and compared to appropriate controls.

RESULTS: Compared to the non-lasered control, TNF- α and VEGF protein were increased in the RPE/choroids in a murine laser-induced CNV model ($p < 0.05$). An intravitreal neutralizing antibody to mouse TNF- α reduced CNV volume, and VEGF protein in the RPE/choroids ($p < 0.01$) and oxidized phospholipids within CNV compared to IgG control ($p < 0.05$). In cultured RPE cells and compared to controls, TNF- α induced ROS generation and increased activation of NOX4, an isoform of NADPH oxidase; both were prevented by pretreatment with the apocynin or VAS2870 or knockdown of p22phox, a subunit of NADPH oxidase. TNF- α treatment increased VEGF expression ($p < 0.001$) and the formation of a transcriptional complex of β -catenin and T-cell transcriptional factor; both were prevented by pretreatment with apocynin or knockdown of p22phox. Inhibition of β -catenin by XAV939, but not the nuclear factor kappa B inhibitor, Bay 11-7082, prevented TNF- α -induced VEGF upregulation.

CONCLUSIONS: Our results support the thinking that TNF- α contributes to CNV by upregulating VEGF production in RPE cells through ROS-dependent activation of β -catenin signaling. These results provide mechanisms of crosstalk between inflammatory mediator, TNF- α , and ROS in RPE cells.

PMID: 26900328 [PubMed - in process] PMCID: PMC4736754

Ophthalmic Genet. 2016 Feb 25;1-8. [Epub ahead of print]

Retinal disease in the C3 glomerulopathies and the risk of impaired vision.

Savige J, Amos L, Ierino F, Mack HG, Symons RC, Hughes P, Nicholls K, Colville D.

BACKGROUND: Dense deposit disease and atypical hemolytic uremic syndrome are often caused by Complement Factor H (CFH) mutations. This study describes the retinal abnormalities in dense deposit disease and, for the first time, atypical haemolytic uremic syndrome. It also reviews our understanding of drusen pathogenesis and their relevance for glomerular disease.

METHODS: Six individuals with dense deposit disease and one with atypical haemolytic uremic syndrome were studied from 2 to 40 years after presentation. Five had renal transplants. All four who had genetic testing had CFH mutations. Individuals underwent ophthalmological review and retinal photography, and in some cases, optical coherence tomography, and further tests of retinal function.

RESULTS: All subjects with dense deposit disease had impaired night vision and retinal drusen or whitish-yellow deposits. Retinal atrophy, pigmentation, and hemorrhage were common. In late disease, peripheral vision was restricted, central vision was distorted, and there were scotoma from sub-retinal choroidal neovascular membranes and atypical serous retinopathy. Drusen were present but less prominent in the young person with atypical uremic syndrome due to a heterozygous CFH mutation.

CONCLUSIONS: Drusen are common in forms of C3 glomerulopathy caused by compound heterozygous or heterozygous CFH mutations. They are useful diagnostically but also impair vision. Drusen have an identical composition to glomerular deposits. They are also identical to the drusen of age-related macular degeneration, and may respond to the same treatments. Individuals with a C3 glomerulopathy should be assessed ophthalmologically at diagnosis, and monitored regularly for vision-threatening complications.

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J Neuroinflammation. 2016 Feb 24;13(1):47.

The broad-spectrum chemokine inhibitor NR58-3.14.3 modulates macrophage-mediated inflammation in the diseased retina.

Fernando N, Natoli R, Valter K, Provis J, Rutar M.

BACKGROUND: The activity of macrophages is implicated in the progression of retinal pathologies such as atrophic age-related macular degeneration (AMD), where they accumulate among the photoreceptor layer and subretinal space. This process is aided by the local expression of chemokines, which furnish these cells with directional cues that augment their migration to areas of retinal injury. While these qualities make chemokines a potential therapeutic target in curtailing damaging retinal inflammation, their wide variety and signalling redundancy pose challenges in broadly modulating their activity. Here, we examine the efficacy of the broad-spectrum chemokine inhibitor NR58-3.14.3-a suppressor of Ccl- and Cxcl- chemokine pathways- in suppressing macrophage activity and photoreceptor death, using a light-induced model of outer retinal atrophy and inflammation.

METHODS: Photo-oxidative damage was induced in SD rats via exposure to 1000 lux of light for 24 h, after which animals were euthanized at 0- or 7-day post-exposure time points. Prior to damage, NR58-3.14.3 was injected intravitreally. Retinas were harvested and evaluated for the effect of NR58-3.14.3 on subretinal macrophage accumulation and cytokine expression profile, as well as photoreceptor degeneration.

RESULTS: We report that intravitreal administration of NR58-3.14.3 reduces the accumulation of macrophages in the outer retina following exposure to light damage, at both 0- and 7-day post-exposure time points. Injection of NR58-3.14.3 also reduced the up-regulation of inflammatory markers including of Il6, Ccl3, and Ccl4 in infiltrating macrophages, which are promoters of their pathogenic activity in the retina. Finally, NR58-3.14.3-injected retinas displayed markedly reduced photoreceptor death following light damage, at both 0 and 7 days post-exposure.

CONCLUSIONS: Our findings indicate that NR58-3.14.3 is effective in inhibiting subretinal macrophage accumulation in light-induced retinal degeneration and illustrate the potential of broad-spectrum chemokine inhibitors as novel therapeutic agents in thwarting retinal inflammation. Although broad-spectrum chemokine inhibitors may not be appropriate for all retinal inflammatory conditions, our results suggest that they may be beneficial for retinal dystrophies in which chemokine expression and subretinal macrophage accumulation are implicated, such as advanced AMD.

PMID: 26911327 [PubMed - in process] PMCID: PMC4765229

Graefes Arch Clin Exp Ophthalmol. 2016 Feb 20. [Epub ahead of print]

Macrophages or retinal pigment epithelium expressing macrophage markers in age-related macular degeneration? Comment on Lad et al. 2015.

Curcio CA, Ach T.

PMID: 26897741 [PubMed - as supplied by publisher]

Epidemiology

Asia Pac J Ophthalmol (Phila). 2016 Feb 24. [Epub ahead of print]

Refractive Error and the Risk of Age-Related Macular Degeneration in the South Korean Population.

Lin SC, Singh K, Chao DL, Lin SC.

PURPOSE: We investigated the association between refractive error and the prevalence of age-related macular degeneration (AMD) in a population-based study.

DESIGN: This was a cross-sectional study.

METHODS: Right eyes were included from 14,067 participants aged 40 years and older with gradable fundus photographs and refraction data from the fourth and the fifth Korea National Health and Nutrition Examination Survey 2008 to 2011. Early and late AMD was graded based on the International Age-Related Maculopathy Epidemiological Study Group grading system. Autorefraction data were collected to calculate spherical equivalent refraction in diopters (D) and classified into 4 groups: hyperopia (≥ 1.0 D), emmetropia (-0.99 to 0.99 D), mild myopia (-1.0 to -2.99 D), and moderate to high myopia (≤ -3.0 D).

RESULTS: After adjustment for potential confounders, each diopter increase in spherical equivalent was associated with a 16% [odds ratio (OR), 1.16; 95% confidence interval (CI), 1.08-1.25] and 18% (OR, 1.18; 95% CI, 1.10-1.27) increased risk of any (early + late) and early AMD, respectively. Mild and moderate to high myopia were associated with lower odds of any and early AMD compared with hyperopia (any AMD: OR, 0.62; 95% CI, 0.4-0.95 for mild myopia; OR, 0.41; 95% CI, 0.21-0.81 for moderate to high myopia; early AMD: OR, 0.63; 95% CI, 0.4-0.99 for mild myopia; OR, 0.36; 95% CI, 0.16-0.77 for moderate to high myopia group). There was no association between refractive status and the likelihood of late AMD ($P = 0.91$).

CONCLUSIONS: Myopia is associated with lower odds of any and early AMD, but not with late AMD in the South Korean population.

PMID: 26914445 [PubMed - as supplied by publisher]

Eye (Lond). 2016 Feb 26. [Epub ahead of print]

The prevalence and risk factors for age-related macular degeneration in rural-urban India, Sankara Nethralaya Rural-Urban Age-related Macular degeneration study, Report No. 1.

Raman R, Pal SS, Ganesan S, Gella L, Vaitheeswaran K, Sharma T.

Purpose: To report the age- and gender-adjusted prevalence rates of early and late age-related maculopathy (ARM) and associated risk factors in rural and urban Indian population.

Methods: A population-based cross-sectional study was carried out in South India between 2009 and 2011. Of the 6617 subjects ≥ 60 years enumerated ones, 5495 (83.04%) participated in the eye examination. A detailed history including data on demographic, socioeconomic, and ocular history was obtained. Participants underwent detailed ophthalmic evaluation including 30° 3-field photograph as per Age-Related Eye Disease Study protocol. The ARM was graded according to the International ARM Epidemiological Study Group.

Results: Age- and gender-adjusted prevalence of early ARM was 20.91% (20.86-20.94) in the rural population and 16.37% (16.32-16.42) in the urban population. Similarly, the prevalence of late ARM was 2.26% (2.24-2.29) and 2.32% (2.29-2.34) in the rural and urban population, respectively. In both rural and urban populations, risk factors that were related to both early and late ARM were age, per year increase (OR, range 1.00-1.08); middle socioeconomic status (OR, range 1.05-1.83); and smokeless tobacco (OR, range 1.11-2.21). Protective factor in both was the presence of diabetes mellitus in all ARM (OR, range 0.34-0.83). Risk factors, only in the rural arm, were female gender (OR, range 1.06-1.64), past smoker (OR, 1.14), and serum low-density lipoprotein cholesterol level (OR, 1.03).

Conclusions: The study reports smokeless tobacco as a risk factor for both early and late ARM and identified a higher prevalence of early ARM in the rural population compared with urban population. Eye advance online publication, 26 February 2016; doi:10.1038/eye.2016.14.

PMID: 26915746 [PubMed - as supplied by publisher]

Genetics

Ophthalmic Genet. 2016 Feb 25:1-6. [Epub ahead of print]

Evaluating VEGFR1 genetic polymorphisms as a predisposition to AMD in a cohort from northern China.

Xiang W, Zhuang W, Chi H, Sheng X, Zhang W, Xue Z, Pan B, Liu Y.

OBJECTIVE: The association among genetic variants in VEGFR1 and a predisposition to age-related macular degeneration (AMD) in a northern cohort from China was evaluated.

METHODS: A retrospective case-control correlation study was conducted on 432 cases and 906 gender- and ethnicity-matched controls. Whole DNA was isolated from peripheral blood samples after the individuals underwent detailed eye examinations. Eight single nucleotide polymorphisms (SNPs) in VEGFR1 genes were genotyped for all individuals using a MALDI-TOF technique. The distribution of genotypes was analyzed for Hardy-Weinberg equilibrium and the relationships among the genotype and allele frequencies with AMD were evaluated by age-adjusted logistic regression analysis. The measurement of linkage disequilibrium (LD) was carried out by Haploview 4.2. Bonferroni testing was employed to correct for multiple comparisons.

RESULTS: Among the SNPs genotyped, p values of six SNPs were less than 0.05 between AMD cases and unaffected controls. However, after Bonferroni correction, the genotype and allele distributions of only two SNPs, rs9554322 and rs9582036 differed significantly between the controls and AMD patients. Further, the rs9554322 CC genotype conferred strong susceptibility to AMD (OR = 6.057, 95% CI: 3.099-11.839). Rs9943922 was also found to be significantly associated with AMD in the distributions for the genotype and allele recessive model ($p = 0.004$). The specific haplotype CA of rs9582036 and rs9554320 was associated with AMD ($p = 0.035$), but the correlation did not remain after correction.

CONCLUSIONS: The SNPs rs9554322, rs9582036 and rs9943922 were correlated with AMD. Gene variants in VEGFR1 were linked to a pronounced emerging risk for AMD in a population in northern China.

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Ophthalmic Genet. 2016 Feb 25:1-6. [Epub ahead of print]

eNOS polymorphisms in neovascular age-related macular degeneration and polypoidal choroidal vasculopathy in a Chinese Han population.

Zuo C, Li M, Zhang X, Chen H, Su Y, Wu K, Wen F.

PURPOSE: To investigate whether common genetic variants in the endothelial nitric oxide synthase gene (eNOS) are associated with neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) in a Chinese Han population.

METHODS: DNA samples were obtained from 157 nAMD patients, 250 PCV patients and 204 healthy control subjects. Tag single nucleotide polymorphisms (SNPs) across the extended eNOS region were selected using data derived from the HapMap project. Genotyping of each tag SNP was performed by Multiplex SNaPshot system and direct DNA sequencing techniques. Genotypes and allele frequencies were evaluated with PLINK software for each group.

RESULTS: Seven SNPs for eNOS, rs1799983, rs1800783, rs3918186, rs3800787, rs3918188, rs7830, and rs3918227, were chosen as tag SNPs. Among these tag SNPs, rs1800783, rs3918186, rs3918188, and rs3918227 were not associated with nAMD or PCV. Rs1799983, rs3800787, and rs7830 was significantly associated with nAMD ($p = 0.0192$, 0.0170 , and 0.0164 , respectively), but not associated with PCV ($p = 0.4852$, 0.4568 , and 0.4014 , respectively). The discovered associations were no longer significant after Bonferroni correction.

CONCLUSIONS: We found no sufficient evidence to support the role of any common eNOS variants in the susceptibility to nAMD or PCV in a Chinese Han population.

PMID: 26914548 [PubMed - as supplied by publisher]

PLoS One. 2016 Feb 26;11(2):e0149978. eCollection 2016.

Prevalence and Genetic Characteristics of Geographic Atrophy among Elderly Japanese with Age-Related Macular Degeneration.

Sakurada Y, Yoneyama S, Sugiyama A, Tanabe N, Kikushima W, Mabuchi F, Kume A, Kubota T, Iijima H.

OBJECTIVE: To investigate the prevalence and genetic characteristics of geographic atrophy (GA) among elderly Japanese with advanced age-related macular degeneration (AMD) in a clinic-based study.

METHODS: Two-hundred and ninety consecutive patients with advanced AMD were classified into typical neovascular AMD, polypoidal choroidal vasculopathy (PCV), retinal angiomatous proliferation (RAP) or geographic atrophy (GA). Genetic variants of ARMS2 A69S (rs10490924) and CFH I62V (rs800292) were genotyped using TaqMan Genotyping Assays. The clinical and genetic characteristics were compared between patients with and without GA.

RESULTS: The number of patients diagnosed as having typical neovascular AMD, PCV, RAP and GA were 98 (33.8%), 151 (52.1%), 22 (7.5%) and 19 (6.6%), respectively. Of 19 patients with GA, 13 patients (68.4%) had unilateral GA with exudative AMD in the contralateral eye. Patients with GA were significantly older, with a higher prevalence of reticular pseudodrusen, bilateral involvement of advanced AMD and T-allele frequency of ARMS2 A69S compared with those with typical AMD and PCV; although there were no differences in the genetic and clinical characteristics among patients with GA and RAP.

CONCLUSIONS: The prevalence of GA was 6.6% among elderly Japanese with AMD. Patients with GA and RAP exhibited genetic and clinical similarities.

PMID: 26918864 [PubMed - in process]

Curr Opin Ophthalmol. 2016 Feb 25. [Epub ahead of print]

Update on ocular gene therapy and advances in treatment of inherited retinal diseases and exudative macular degeneration.

Garoon RB, Stout JT.

PURPOSE OF REVIEW: The purpose of this article is to provide an update on ocular gene therapy and discuss current active clinical trials.

RECENT FINDINGS: The main target for ocular gene therapy involves the retinal pigment epithelium or photoreceptors. The most common method to deliver viral vectors to these cells includes intravitreal injection, subretinal injection, or access from the suprachoroidal space. Recombinant adeno-associated virus and lentivirus can be engineered to maximize gene delivery to specific targets. There are several clinical trials currently aimed at treating inherited and retinal diseases with gene therapy via viral vectors.

SUMMARY: Recent advances in gene therapy have allowed for a better understanding of inherited and proliferative retinal diseases. New techniques have been developed to improve delivery of viral vectors to their cellular targets. There are currently multiple active clinical trials involving gene therapy underway with promising preliminary results.

PMID: 26918787 [PubMed - as supplied by publisher]

Stem cells

J Biomed Mater Res A. 2016 Feb 23. [Epub ahead of print]

Honeycomb porous films as permeable scaffold materials for human embryonic stem cell-derived retinal pigment epithelium.

Calejo MT, Ilmarinen T, Jongprasitkul H, Skottman H, Kellomäki M.

Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness in developed countries, characterised by the degeneration of the retinal pigment epithelium (RPE), a pigmented cell monolayer that closely interacts with the photoreceptors. RPE transplantation is thus considered a very promising therapeutic option to treat this disease. In this work, porous honeycomb-like films are for the first time investigated as scaffold materials for human embryonic stem cell-derived retinal pigment epithelium (hESC-RPE). By changing the conditions during film preparation, it was possible to produce films with homogeneous pore distribution and adequate pore size ($\sim 3\text{-}5\text{ }\mu\text{m}$), i.e. large enough to ensure high permeability but small enough to enable cell adherence and spreading. A brief dip-coating procedure with collagen type IV enabled the homogeneous adsorption of the protein to the walls and bottom of pores, increasing the hydrophilicity of the surface. hESC-RPE adhered and proliferated on all the collagen-coated materials, regardless of small differences in pore size. The differentiation of hESC-RPE was confirmed by the detection of specific RPE protein markers. These results suggest that the porous honeycomb films can be promising candidates for hESC-RPE tissue engineering, importantly enabling the free flow of ions and molecules across the material. This article is protected by copyright. All rights reserved.

PMID: 26914698 [PubMed - as supplied by publisher]

Diet, lifestyle and low vision

PLoS One. 2016 Feb 22;11(2):e0149219. eCollection 2016.

Dynamic Drusen Remodelling in Participants of the Nutritional AMD Treatment-2 (NAT-2) Randomized Trial.

Querques G, Merle BM, Pumariega NM, Benlian P, Delcourt C, Zourdani A, Leisy HB, Lee MD, Smith RT, Souied EH.

PURPOSE: To evaluate the dynamic remodeling of drusen in subjects with unilateral neovascular age-related macular degeneration (AMD) receiving a three-year course of oral docosahexaenoic acid (DHA) or placebo.

SETTING: Institutional setting.

METHODS: Three hundred subjects with age-related maculopathy and neovascular AMD in the fellow eye were randomly assigned to receive either 840 mg/day DHA or placebo for 3 years. Main outcome measures of this post-hoc sub-group analysis were progression of drusen number, total diameter, and total area on fundus photography, and their association with DHA supplementation, socio-demographic and genetic characteristics.

RESULTS: Drusen progression was analyzed in 167 subjects that did not develop CNV (87 that received DHA and 80 that received placebo). None of the drusen remodeling outcomes were significantly associated with DHA supplementation. Total drusen diameter reduction in the inner subfield was significantly associated with age (older patients: $r = -0.17$; $p = 0.003$). Women showed a tendency to decreased total drusen diameter in the inner subfield with CFH polymorphism ($p = 0.03$), where women with TT genotype tended to have a greater reduction in drusen diameter than other genotypes (CC and CT). Drusen area in the inner subfield was more reduced in older patients ($r = -0.17$) and in women ($p = 0.01$). Drusen number showed no significant trends.

CONCLUSIONS: Dynamic drusen remodeling with net reduction in drusen load over three years was found in patients with exudative AMD in one eye and drusen in the other eye (study-eye). This reduction was correlated with increased age and female gender, and showed a tendency to be influenced by CFH genotype, but did not appear to be affected by DHA supplementation.

PMID: 26901353 [PubMed - in process]

Clin Dermatol. 2016 Mar-Apr;34(2):276-85. Epub 2015 Nov 22.

An eye on nutrition: The role of vitamins, essential fatty acids, and antioxidants in age-related macular degeneration, dry eye syndrome, and cataract.

McCusker MM, Durrani K, Payette MJ, Suchecki J.

Abstract: Visual impairment is a global epidemic. In developing countries, nutritional deficiency and cataracts continue to be the leading cause of blindness, whereas age-related macular degeneration (AMD) and cataracts are the leading causes in developed nations. The World Health Organization has instituted VISION 2020: "The Right to Sight" as a global mission to put an end to worldwide blindness. In industrialized societies, patients, physicians, researchers, nutritionists, and biochemists have been looking toward vitamins and nutrients to prevent AMD, cataracts, and dry eye syndrome (DES). Nutrients from the AREDS2 study (lutein, zeaxanthin, vitamin C, vitamin E, zinc, copper, eicosapentanoic acid [EPA], and docosahexanoic acid [DHA]) set forth by the National Institutes of Health remain the most proven nutritional therapy for reducing the rate of advanced AMD. Omega-3 fatty acids, especially DHA, have been found to improve DES in randomized clinical trials. Conflicting results have been seen with regard to multivitamin supplementation on the prevention of cataract.

PMID: 26903189 [PubMed - in process]

Food Funct. 2016 Feb 25. [Epub ahead of print]

Postprandial dietary fatty acids exert divergent inflammatory responses in retinal-pigmented epithelium cells.

Montserrat-de la Paz S, Naranjo MC, Bermudez B, Lopez S, Moreda W, Abia R, Muriana FJ.

Abstract: Postprandial triglyceride-rich lipoproteins (TRLs) lead to a complex series of events that are potentially oxidative and inflammatory. The main goal of this study was to characterize the influence of postprandial TRLs with different fatty acid compositions (mainly SFAs, MUFAs or MUFAs plus omega-3 PUFAs) on oxidative and inflammatory markers in RPE cells, which play a pivotal role in age-related macular degeneration (AMD). Compared to TRL-SFAs, TRL-MUFAs and TRL-MUFAs plus omega-3 PUFAs decreased the production of ROS and nitrite, and the gene expression and secretion of IL-1 β , IL-6, TNF- α , IFN γ and VEGF. For the first time we show that postprandial TRLs are metabolic entities able to induce RPE oxidative stress and inflammation in a fatty acid-dependent manner, TRL-SFAs >>> TRL-MUFAs = TRL-MUFAs plus omega-3 PUFAs. These exciting findings open new opportunities for developing novel nutritional strategies with olive oil as the principal dietary source of oleic acid to prevent the development and progression of AMD.

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Ophthalmic Physiol Opt. 2016 Feb 26. [Epub ahead of print]

A survey of UK optometry trainees' smoking cessation training.

Lorenatto F, Harper AM, Francis JJ, Lawrenson JG.

BACKGROUND: Smoking is a risk factor for a number of eye conditions, including age-related macular degeneration, cataracts and thyroid eye disease. Smoking cessation interventions have been shown to be highly cost-effective when delivered by a range of healthcare professionals. Optometrists are well placed to deliver smoking cessation advice to a wide population of otherwise healthy smokers. Yet optometrists remain a relatively neglected healthcare professional group in smoking cessation research and policy. Surveys of UK medical/nursing schools and of optometrists' training internationally demonstrate significant deficits in current curricular coverage regarding smoking cessation. This study aimed to identify the extent of smoking cessation training in UK optometry trainees' undergraduate and pre-registration training.

METHODS: All undergraduate optometry schools in the UK (n = 9) were invited to participate in a web-based survey of their curricular coverage and assessment related to smoking cessation, and of perceived barriers to delivering smoking cessation training. A content analysis of the College of Optometrists Scheme for Registration Trainee Handbook 2014 was conducted to identify competence indicators related to smoking cessation.

RESULTS: Nine undergraduate optometry schools (100%) responded to the survey. The majority reported dedicating limited hours (0-3) to teaching smoking cessation, and predominantly focused on teaching the harmful effects of smoking (89%). Only one school provides practical skills training for delivering evidence-based smoking cessation interventions, including very brief advice. The majority of schools (78%) reported that they did not formally examine students on their knowledge or skills for supporting smoking cessation, and rated confidence in their graduates' abilities to deliver smoking cessation interventions as 'poor' (78%). Lack of knowledge amongst staff was identified as the key barrier to teaching about smoking cessation support. The pre-registration competency framework does not include any competence indicators related to providing support for quitting smoking.

CONCLUSIONS: There are substantial gaps in the current curricula of UK optometry training, particularly regarding practical skills for supporting smoking cessation. Increased curricular coverage of these issues is essential to ensure trainee optometrists are adequately trained and competent in supporting patients to quit smoking.

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