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MD Research News

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Drug treatment

BMC Ophthalmol. 2015 Apr 11;15(1):40. [Epub ahead of print]

Short-term outcomes of switching anti-VEGF agents in eyes with treatment-resistant wet AMD.

Batioglu F, Demirel S, Özmert E, Abdullayev A, Bilici S.

BACKGROUND: To investigate the short-term outcomes of treatment with intravitreal aflibercept in cases with wet age-related macular degeneration (AMD) resistant to ranibizumab.

METHODS: The study included patients who had been undergoing follow-up for a minimum of three months at the Ankara University Faculty of Medicine Ophthalmology Department's Retina Unit with a diagnosis of wet AMD. All cases had received intravitreal aflibercept injection due to the presence of intraretinal/subretinal fluid and pigment epithelial detachment (PED), as detected by optical coherence tomography (OCT), despite having received intravitreal ranibizumab. Medical records of the cases were investigated retrospectively and the demographic data, treatments administered before aflibercept injection, best-corrected visual acuity (BCVA) before and after aflibercept injection, central macular thickness (CMT), and the presence of intraretinal/subretinal fluid and the height and presence of PED were recorded.

RESULTS: A total of 29 eyes from 11 females and 17 males were included in the study. The mean age was 73.89 ± 7.49 (62-92). The average number of intraocular injections administered before aflibercept injection was 11.75 ± 5.73 (6-25). The mean duration of follow-up following aflibercept injection was 4.55 ± 2.14 (3-11) months, with a mean of 3.44 ± 0.73 (3-5) aflibercept injections during this period. The mean BCVA values before and after aflibercept injection were found to be 0.83 and 0.77 LogMAR, respectively. The mean CMT values before and after aflibercept injection were 471.3 (97-1365) and 345.1 (97-585) microns, respectively ($p < 0.001$). The PED height before and after aflibercept injection was 350.4 ± 151.7 (129-793) and 255.52 ± 156.8 (0-528) microns, respectively ($p < 0.05$).

CONCLUSION: Switching to intravitreal aflibercept appears to be an effective treatment modality for patients with AMD who are resistant to ranibizumab. While anatomic success including the effect of reducing the PED height was achieved in the short term following aflibercept injection in all cases, no concomitant increase in visual acuity occurred. This is attributed to the long-term presence of chronic fluid and the development of scar tissue before the treatment.

PMID: 25885684 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2015 Mar 29;15(1):30.

Full thickness macular hole case after intravitreal aflibercept treatment.

Oshima Y, Apte RS, Nakao S, Yoshida S, Ishibashi T.

BACKGROUND: The pathogenesis of macular hole formation is widely accepted as a tractional force at the vitreo-retinal interface in fovea. We report a case of macular hole after intravitreous aflibercept injection for age-related macular degeneration (AMD) associated with contraction of the retinal pigment epithelium (RPE) at the edge of a fibrovascular pigment epithelial detachment (PED).

CASE PRESENTATION: A 94-year old man with neovascular AMD affecting his left eye accompanied by a fibrovascular PED was examined for severe vision loss. Although RPE tear in his left eye was identified before the first aflibercept intravitreous injection performed in order to treat neovascular AMD, he received three aflibercept injections as induction treatment. After induction treatment, a full thickness macular hole was identified associated with the contracted rolled RPE edge beneath the retina.

CONCLUSION: Macular hole is commonly formed associated with tangential vitreous traction. Current report suggests that rapid contraction of the RPE underneath the retina can be one of the causes of a macular hole, and one of the side effects of anti-VEGF therapy for neovascular AMD.

PMID: 25881212 [PubMed - in process] PMCID: PMC4381494

BMC Ophthalmol. 2015 Apr 11;15(1):39. [Epub ahead of print]

Bevacizumab treatment for neovascular age-related macular degeneration in the setting of a clinic: "real life" long-term outcome.

Beykin G, Grunin M, Averbukh E, Banin E, Hemo Y, Chowers I.

BACKGROUND: To evaluate the long-term outcome of bevacizumab therapy for neovascular age related macular degeneration (NVAMD) in the setting of a clinic.

METHODS: Consecutive group of NVAMD patients who were treated in a single 3rd referral center with bevacizumab using a loading dosage of 3 monthly injections followed by variable dosing for at least 48 months were retrospectively evaluated. Genotyping was performed for CFH (rs1061170), HTRA1 (rs1200638), and C3 (rs2230199). Main outcome measures included functional and morphological treatment outcomes as well as their risk allele associations.

RESULTS: Out of 128 patients who started bevacizumab treatment over 4 years before the study endpoint [mean (±SD): 60 ± 10.9 months], 75 eyes of 67 (52.3%) patients, were still followed. Mean best corrected visual acuity (BCVA) (LogMAR ± SEM) improved from 0.66 ± 0.07 at baseline to 0.48 ± 0.05 ($p = 0.012$) at 1 year, but deteriorated from the 3rd year on and at the final exam reduced to 0.69 ± 0.07 ($p = 0.6$, compared with initial BCVA). Macular thickness mirrored visual acuity (VA) changes showing initial thinning followed by thickening from the 3rd year on. Individuals carrying the CFH risk -allele had a mean thickening (microns ± SEM) of 66.9 ± 70.4 versus a mean thinning of 76.8 ± 22 in non-carriers ($p = 0.015$).

CONCLUSIONS: Bevacizumab therapy for NVAMD using a flexible treatment algorithm in a "real life" clinical setting initially obtained VA gain and thinning of the macula that were maintained for two years, but were lost later on.

PMID: 25881145 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2015 Mar 29;15(1):31.

Ranibizumab for macular edema secondary to retinal vein occlusion: a meta-analysis of dose effects and comparison with no anti-VEGF treatment.

Song WT, Xia XB.

BACKGROUND: To compare the efficacy and tolerability of intravitreal ranibizumab (IVR) 0.5 mg or 0.3 mg with non-anti-vascular endothelial growth factor (VEGF), and to compare the efficacy of IVR 0.5 mg with IVR 0.3 mg in the treatment of macular edema secondary to retinal vein occlusion.

METHODS: Relevant studies were selected after an extensive search using the PubMed, EMBASE, Web of Science, and Cochrane Library databases. Outcomes of interest included visual outcomes, anatomic variables, and adverse events.

RESULTS: Four randomized controlled trials (RCTs) met our inclusion criteria. IVR 0.5 mg produced a significantly higher improvement in visual acuity at six months, with pooled weighted mean differences (WMDs) of 12.30 early treatment diabetic retinopathy study (ETDRS) letters (95% CI:10.03, 14.58) ($P < 0.001$),and led to a higher proportion of patients gaining ≥15 letters (RR, 2.36; 95%CI: 1.86, 2.99; $P < 0.001$) at the follow-up endpoint, compared with non-anti-VEGF. A more obvious reduction in central foveal thickness (CFT) was observed in the IVR 0.5 mg group than the non-anti-VEGF group, and the mean difference in CFT was statistically significant (WMD, -216.86 μm; 95%CI: -279.01, -154.71; $P < 0.001$). A similar efficacy was found between the IVR 0.3 mg group and the non-anti-VEGF group. No significant differences were found between IVR 0.5 mg and 0.3 mg. The incidence of iris neovascularization in the non -anti-VEGF group was significantly higher than that of the IVR group.

CONCLUSIONS: IVR 0.5 mg or 0.3 mg was more effective than sham injection and laser treatment. IVR 0.3 mg is as effective as IVR 0.5 mg in the treatment of macular edema secondary to retinal vein occlusion.

PMID: 25881069 [PubMed - in process] PMCID: PMC4381461

Trials. 2015 Mar 10;16(1):85.

Comparing different dosing regimens of bevacizumab in the treatment of neovascular macular degeneration: study protocol for a randomised controlled trial.

Foss AJ, Childs M, Reeves BC, Empeslidis T, Tesha P, Dhar-Munshi S, Mughal S, Culliford L, Rogers CA, Tan W, Montgomery A.

BACKGROUND: Bevacizumab (Avastin®) is as effective as ranibizumab (Lucentis®) in the treatment of neovascular age-related macular degeneration (nAMD). However it has two important structural differences. First, it has two active sites instead of one; second, it retains the Fc portion of the antibody which would be expected to confer a significantly longer half-life. These agents have been associated with systemic complications including strokes, so it is desirable to use the smallest effective dose. Furthermore, the standard dosing regimen requires monthly hospital visits, which present a significant challenge both to the hospital services and to the patients (who are elderly).

METHODS/DESIGN: Patients ≥50 years who are eligible for anti-vascular endothelial growth factor (VEGF) treatment of nAMD in the NHS, who are either newly referred for treatment or have reactivation of nAMD and who have not received treatment to either eye for the previous six months. We have designed a factorial multi-centre masked randomised controlled trial using bevacizumab as the intervention, with patients randomised to one of four arms: to standard or low dose and to monthly or two-monthly patient review. The aim is to recruit sufficient patients (around 1,000) to obtain 304 patients meeting the endpoint over a four-year period. The primary endpoint is time to treatment failure to be analysed using Cox regression.

DISCUSSION: This randomised control trial will show if half dose and two monthly as required is as effective as full dose and monthly regimes. A two monthly as required regimen of Bevacizumab would significantly reduce both the cost and the service delivery burden for the treatment of nAMD while a reduced dose would be expected to enhance the safety profile of this treatment regime.

PMID: 25873213 [PubMed - in process] PMCID: PMC4376508

Br J Ophthalmol. 2015 Apr 15. [Epub ahead of print]

Change in choroidal thickness after intravitreal aflibercept in pretreated and treatment-naive eyes for neovascular age-related macular degeneration.

Mazaraki K, Fassnacht-Riederle H, Blum R, Becker M, Michels S.

AIM: Evaluation of effects of intravitreal aflibercept therapy on choroidal thickness (CT) in neovascular age-related macular degeneration.

METHODS: Retrospective cohort study evaluating the change in CT following a loading dose of three intravitreal aflibercept injections at 4 weeks interval. Pretreated and treatment-naive eyes as well as untreated fellow eyes were evaluated at five retinal locations (subfoveal, 300 and 2500 µm nasal and temporal to the fovea) using spectral domain optical coherence tomography prior to and 4 weeks after a loading dose of three intravitreal aflibercept injections.

RESULTS: A total of 84 treated eyes (61 pretreated, 23 treatment naive) and 48 fellow eyes were enrolled into the study. Treatment-naive and pretreated eyes showed a significant reduction in CT at all retinal locations. The effect was more pronounced in treatment-naive eyes. In the pretreated group, the mean reduction in CT was greatest at 2500 µm temporal to the fovea at 10.7 µm compared with 22.4 at 300 µm nasal to the fovea in the treatment-naive group. Only the fellow eyes in the treatment-naive group showed a significant CT reduction 12 weeks after initiation of therapy to the partner eye.

CONCLUSIONS: Aflibercept induces a reduction in CT in treatment-naive and pretreated eyes with neovascular age-related macular degeneration. There is some evidence of a systemic effect of aflibercept reflected by CT reduction in untreated fellow eyes.

PMID: 25877895 [PubMed - as supplied by publisher]

Optom Vis Sci. 2015 Mar 31. [Epub ahead of print]

Intravitreal Aflibercept after Bilateral Bevacizumab-Induced Iritis.

Skorin L Jr, Genereux L.

PURPOSE: To present a case of neovascular age-related macular degeneration treated with aflibercept intravitreal injections after bilateral bevacizumab injections, administered on separate dates, resulted in bilateral iritis.

CASE REPORT: A 73-year-old woman with a previous history of two episodes of nongranulomatous iritis in her right eye that was believed to be associated with her systemic diagnosis of rheumatoid arthritis was treated with intravitreal bevacizumab injections for bilaterally occurring neovascular age-related macular degeneration. Initial bevacizumab injections in each eye administered sequentially over a week's time resulted in immediate-onset nongranulomatous iritis in each eye. Subsequent intravitreal injections of aflibercept were administered, and therapeutic benefit was achieved without occurrence of iritis.

CONCLUSIONS: In cases where intravitreal bevacizumab results in anterior uveitis, aflibercept may be a safe alternative therapeutic choice for the treatment of neovascular age-related macular degeneration.

PMID: 25871873 [PubMed - as supplied by publisher]

Ophthalmic Res. 2015 Apr 9;53(4):194-199. [Epub ahead of print]

Emerging Therapeutic Options in Age-Related Macular Degeneration.

Querques G, Capuano V, Frascio P, Bandello F, Souied EH.

Abstract: Intravitreal injection of anti-VEGF drugs currently represents the standard of treatment for exudative age-related macular degeneration. Several therapeutic options including steroids, inhibitors of

complement factors, anti-platelet-derived growth factor agents, new anti-VEGF drugs, designed ankyrin repeat proteins, sustained drug delivery devices as an alternative to intravitreal injections and encapsulated cell technology are the objects of several studies and trials worldwide in association with anti-VEGF therapy or not. Expectations are that such efforts will help overcome limitations of current therapy with anti-VEGF, extending the duration of effects and hopefully contributing to the regression of neovascular lesions.

PMID: 25871486 [PubMed - as supplied by publisher]

BMJ Case Rep. 2015 Apr 13;2015.

Anti-VEGF therapy in a silicone oil-filled myopic eye with choroidal neovascularisation.

Chhablani J, Narayanan R.

Abstract: A 33-year-old man presented with vision loss in his right eye due to rhegmatogenous retinal detachment, for which he underwent pars plana vitrectomy with silicone oil injection. Three months later, the patient presented with sudden vision loss. On examination, his visual acuity was 20/200 with presence of subretinal haemorrhage with attached retina and silicone oil in situ. Fluorescein angiography confirmed the diagnosis of choroidal neovascularisation (CNV). The patient underwent intravitreal ranibizumab injection (0.5 mg per 0.05 mL). He subsequently underwent oil removal along with intravitreal bevacizumab injection (1.25 mg per 0.05 mL). The CNV completely regressed. At 7 years follow-up, the patient's best corrected visual acuity was 20/50 with attached retina and macular scar due to regressed CNV. His other eye was within normal limits throughout the follow-up period. This unique case demonstrates the successful outcome of intravitreal ranibizumab injection in a silicone oil-filled eye with myopic CNV.

PMID: 25870215 [PubMed - in process]

Ophthalmology. 2015 Apr 11. [Epub ahead of print]

Predictors of Functional and Anatomic Outcomes in Patients with Diabetic Macular Edema Treated with Ranibizumab.

Sophie R, Lu N, Campochiaro PA.

OBJECTIVE: To investigate baseline predictors of month 24 best-corrected visual acuity (BCVA) and central foveal thickness (CFT) in patients with diabetic macular edema (DME) treated monthly with ranibizumab or sham.

DESIGN: Post hoc analysis of DME patients in 2 identical phase 3 studies.

PARTICIPANTS: Patients randomized to ranibizumab (n = 502) or sham (n = 257).

METHODS: Multivariate regression on predictors with $P < 0.20$ in univariate logistic regression using backward selection to retain predictors with $P < 0.05$.

MAIN OUTCOME MEASURES: Patient characteristics correlating with month 24 BCVA in Early Treatment Diabetic Retinopathy Study letter score ≥70 (20/40) or ≤50 (20/100), gain or loss from baseline BCVA of ≥15, or CFT ≤250 μm.

RESULTS: Baseline predictors of BCVA ≥20/40 in ranibizumab-treated patients were good BCVA, submacular fluid, no cardiovascular disease, no scatter photocoagulation, and male gender, whereas in sham-treated patients, they were mild increase in CFT, presence of hard exudates in center subfield, and absence of renal disease. Predictors of improvement in BCVA letter score ≥15 in ranibizumab-treated patients were poor BCVA, submacular fluid, young age, and short diabetes duration, and those in sham-treated patients were poor BCVA, young age, and mild increase in CFT. Predictors of resolution of edema (CFT ≤250 μm) in ranibizumab-treated patients were mild foveal thickening and prominent subfoveal fluid, and those in sham-treated patients were poor BCVA, mild foveal thickening, and statin usage. Month 24 BCVA ≤20/100 was predicted by poor baseline BCVA in ranibizumab-treated patients, and by poor baseline

BCVA, large intraretinal cystoid spaces, renal disease, and absence of hypercholesterolemia in sham-treated patients. Loss of BCVA ≥15 letters was predicted in sham-treated patients by submacular fluid, intraretinal cystoid spaces, and renal disease.

CONCLUSIONS: Patients with DME and submacular fluid, intraretinal cysts, severe thickening, or renal disease respond poorly when untreated and respond well to ranibizumab treatment. Elimination of submacular fluid, intraretinal cysts, and severe thickening are important goals of DME treatment, and in patients with renal disease, treatment should be very aggressive, with a goal of eliminating all macular fluid.

PMID: 25870079 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2015 Apr 12. [Epub ahead of print]

Effect of posterior vitreous detachment on aqueous humor level of vascular endothelial growth factor in exudative age-related macular degeneration patients.

Nomura Y, Takahashi H, Tan X, Fujino Y, Kawashima H, Yanagi Y.

BACKGROUND: To investigate the association of posterior vitreous detachment (PVD) with aqueous levels of vascular endothelial growth factor (VEGF) in eyes with exudative age-related macular degeneration (AMD).

METHODS: This is a prospective comparative study. Subjects are 33 eyes with exudative AMD. PVD was examined by B-mode ultrasonography and the subjects were divided into a complete PVD group (PVD group) or a group with partial or no PVD (without PVD group). At the beginning of intravitreal injection of ranibizumab, aqueous humor was collected and the concentration of VEGF was measured using ELISA. The concentration was compared between the two groups.

RESULTS: Complete PVD was observed in 13 (39 %) eyes. The mean concentration of VEGF was 58 pg/ml in the PVD group and 91 pg/ml in the without PVD group. Multiple regression analysis revealed that the concentration of VEGF was significantly lower in the eyes with PVD than in those without PVD independent of age and sex (P = 0.02).

CONCLUSIONS: Complete PVD is related to the lower concentration of aqueous VEDF in AMD eyes.

PMID: 25863675 [PubMed - as supplied by publisher]

Eye (Lond). 2015 Apr 17. [Epub ahead of print]

Defining response to anti-VEGF therapies in neovascular AMD.

Amoaku WM, Chakravarthy U, Gale R, Gavin M, Ghanchi F, Gibson J, Harding S, Johnston RL, Kelly S, Lotery A, Mahmood S, Menon G, Sivaprasad S, Talks J, Tufail A, Yang Y.

Abstract: The introduction of anti-vascular endothelial growth factor (anti-VEGF) has made significant impact on the reduction of the visual loss due to neovascular age-related macular degeneration (n-AMD). There are significant inter-individual differences in response to an anti-VEGF agent, made more complex by the availability of multiple anti-VEGF agents with different molecular configurations. The response to anti-VEGF therapy have been found to be dependent on a variety of factors including patient's age, lesion characteristics, lesion duration, baseline visual acuity (VA) and the presence of particular genotype risk alleles. Furthermore, a proportion of eyes with n-AMD show a decline in acuity or morphology, despite therapy or require very frequent re-treatment. There is currently no consensus as to how to classify optimal response, or lack of it, with these therapies. There is, in particular, confusion over terms such as 'responder status' after treatment for n-AMD, 'tachyphylaxis' and 'recalcitrant' n-AMD. This document aims to provide a consensus on definition/categorisation of the response of n-AMD to anti-VEGF therapies and on the time points at which response to treatment should be determined. Primary response is best determined at 1 month following the last initiation dose, while maintained treatment (secondary) response is determined any

time after the 4th visit. In a particular eye, secondary responses do not mirror and cannot be predicted from that in the primary phase.

Morphological and functional responses to anti-VEGF treatments, do not necessarily correlate, and may be dissociated in an individual eye. Furthermore, there is a ceiling effect that can negate the currently used functional metrics such as >5 letters improvement when the baseline VA is good (ETDRS>70 letters). It is therefore important to use a combination of both the parameters in determining the response.The following are proposed definitions: optimal (good) response is defined as when there is resolution of fluid (intraretinal fluid; IRF, subretinal fluid; SRF and retinal thickening), and/or improvement of >5 letters, subject to the ceiling effect of good starting VA. Poor response is defined as <25% reduction from the baseline in the central retinal thickness (CRT), with persistent or new IRF, SRF or minimal or change in VA (that is, change in VA of 0+4 letters). Non-response is defined as an increase in fluid (IRF, SRF and CRT), or increasing haemorrhage compared with the baseline and/or loss of >5 letters compared with the baseline or best corrected vision subsequently. Poor or non-response to anti-VEGF may be due to clinical factors including suboptimal dosing than that required by a particular patient, increased dosing intervals, treatment initiation when disease is already at an advanced or chronic stage), cellular mechanisms, lesion type, genetic variation and potential tachyphylaxis); non-clinical factors including poor access to clinics or delayed appointments may also result in poor treatment outcomes.

In eyes classified as good responders, treatment should be continued with the same agent when disease activity is present or reactivation occurs following temporary dose holding. In eyes that show partial response, treatment may be continued, although re-evaluation with further imaging may be required to exclude confounding factors. Where there is persistent, unchanging accumulated fluid following three consecutive injections at monthly intervals, treatment may be withheld temporarily, but recommenced with the same or alternative anti-VEGF if the fluid subsequently increases (lesion considered active). Poor or non-response to anti-VEGF treatments requires re-evaluation of diagnosis and if necessary switch to alternative therapies including other anti-VEGF agents and/or with photodynamic therapy (PDT). Idiopathic polypoidal choroidopathy may require treatment with PDT monotherapy or combination with anti-VEGF. A committee comprised of retinal specialists with experience of managing patients with n-AMD similar to that which developed the Royal College of Ophthalmologists Guidelines to Ranibizumab was assembled. Individual aspects of the guidelines were proposed by the committee lead (WMA) based on relevant reference to published evidence base following a search of Medline and circulated to all committee members for discussion before approval or modification. Each draft was modified according to feedback from committee members until unanimous approval was obtained in the final draft. A system for categorising the range of responsiveness of n-AMD lesions to anti-VEGF therapy is proposed. The proposal is based primarily on morphological criteria but functional criteria have been included. Recommendations have been made on when to consider discontinuation of therapy either because of success or futility. These guidelines should help clinical decision-making and may prevent over and/or undertreatment with anti-VEGF therapy.

PMID: 25882328 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 May;159(5):996-7. doi: 10.1016/j.ajo.2015.02.011.

One-year outcomes of aflibercept in recurrent or persistent neovascular age-related macular degeneration.

Iacono P, Battaglia Parodi M, Bandello F.

PMID: 25867595 [PubMed - in process]

Other treatment & diagnosis

Clin Ophthalmol. 2015 Apr 1;9:563-74. eCollection 2015.

Recent developments in the management of dry age-related macular degeneration.

Buschini E, Fea AM, Lavia CA, Nassisi M, Pignata G, Zola M, Grignolo FM.

Abstract: Dry age-related macular degeneration (AMD), also called geographic atrophy, is characterized by the atrophy of outer retinal layers and retinal pigment epithelium (RPE) cells. Dry AMD accounts for 80% of all intermediate and advanced forms of the disease. Although vision loss is mainly due to the neovascular form (75%), dry AMD remains a challenge for ophthalmologists because of the lack of effective therapies. Actual management consists of lifestyle modification, vitamin supplements, and supportive measures in the advanced stages. The Age-Related Eye Disease Study demonstrated a statistically significant protective effect of dietary supplementation of antioxidants (vitamin C, vitamin E, beta-carotene, zinc, and copper) on dry AMD progression rate. It was also stated that the consumption of omega-3 polyunsaturated fatty acids, such as docosahexaenoic acid and eicosapentaenoic acid, has protective effects. Other antioxidants, vitamins, and minerals (such as crocetin, curcumin, and vitamins B9, B12, and B6) are under evaluation, but the results are still uncertain. New strategies aim to 1) reduce or block drusen formation, 2) reduce or eliminate inflammation, 3) lower the accumulation of toxic by-products from the visual cycle, 4) reduce or eliminate retinal oxidative stress, 5) improve choroidal perfusion, 6) replace/repair or regenerate lost RPE cells and photoreceptors with stem cell therapy, and 7) develop a target gene therapy.

PMID: 25878491 [PubMed] PMCID: PMC4388086

Zhonghua Yan Ke Za Zhi. 2015 Jan;51(1):70-3.

[Clinical characteristics of reticular pseudodrusen].[Article in Chinese]

Zheng S, Lei B.

Abstract: Reticular pseudodrusen (RPD) has recently been identified as a particular yellowish interlacing network of oval or round lesion in the fundus of aged retinal degeneration patients. RPD can be easily misdiagnosed as typical drusen. However, a large number of observations indicated that RPD and typical drusen are different in distribution, morphological features and pathophysiological processes. The diagnosis of RPD relies on multiple fundus examinations including fundus autofluorescence, infrared reflectance and spectral-domain optical coherence tomography. RPD may be associated with age-related macular degeneration, choroidal neovascularization and geographic atrophy, but the prevalence of RPD is found low in polypoidalchoroidalvasculopathycases. Differential diagnosis of RPD and drusen may affect the treatment and prognosis of these conditions. Thus a careful long-term follow-up is mandatory for these patients.

PMID: 25877713 [PubMed - in process]

Vestn Oftalmol. 2015 Jan-Feb;131(1):5-11.

[Choroidal nevi: clinical features]. [Article in Russian]

[No authors listed]

Abstract: The prevalence of choroidal nevi (CN) ranges from 1% to 10%. It may be hard to differentiate a small melanoma from an atypical ("malignatized") CN, which occupies an intermediate position between typical nevi and actual melanomas and can be referred to as "progressive" or "suspicious". The risk of malignant transformation of a CN ranges from 0.78% to 7%, thus necessitating the need for a detailed description of its clinical features.

OBJECTIVE: To study clinical features of choroidal nevi in conjunction with their growth patterns.

MATERIAL AND METHODS: A total of 80 patients (84 eyes) with choroidal nevi were studied, including 23 men and 57 women aged 65.33±3.26 years on average. The follow-up period was 12-48 months. In 26 cases (30.95%) age-related macular degeneration (AMD) was also present.

RESULTS: Choroidal nevus is generally more common in women (71.25%). The right eye was involved in 36 cases, the left--in 48. Bilateral CN was diagnosed in 5% of cases. The follow-up period was 12-48 months. The nevi were mostly located in the juxtapapillary (11.9%) and macular (29.76%) regions. In 10 eyes they spread to the parafovea and foveola. The shape was typically round (73.8%), in the rest of cases --oval (26.2%). The size at presentation varied from 1 mm to 9 mm (2.93 mm on average). Diagnostic features of a stationary nevus (does not require a follow-up) have been identified. Nevus enlargement and changes in the overlying retina are indicative of progression.

CONCLUSION: On the basis of clinical presentation all choroidal nevi can be classified as either stationary or progressing. If progression is suspected, a close follow-up is required. Progressive destruction of the overlying retina and early signs of visual impairment are risk factors for melanoma development.

PMID: 25872380 [PubMed - in process]

Stem Cells. 2015 Apr 13. [Epub ahead of print]

Human iPSC-Derived Neural Progenitors Preserve Vision in an AMD-like Model.

Tsai Y, Lu B, Bakondi B, Girman S, Sahabian A, Sareen D, Svendsen CN, Wang S.

Abstract: Pluripotent stem cell derived retinal pigment epithelial (RPE) cells are currently being tested for cell replacement in late-stage age-related macular degeneration (AMD). However, preserving vision at early -stages may also be possible. Here we demonstrate that transplantation of neural progenitor cells (NPCs) derived from induced pluripotent stem cells (iNPCs) limits disease progression in the Royal College of Surgeons (RCS) rat, a preclinical model of AMD. Grafted-iNPCs survived, remained undifferentiated, and distributed extensively in a laminar fashion in the subretinal space. Retinal pathology resulting from the accumulation of undigested photoreceptor outer segments (POS) was significantly reduced in iNPC-injected rats compared with controls. Phagosomes within grafted-iNPCs contained POS, suggesting that iNPCs had compensated for defective POS phagocytosis by host-RPE. The iNPC-treated eyes contained 6 -8 rows of photoreceptor nuclei that spanned up to 5 mm in length in transverse retinal sections, compared with only one row of photoreceptors in controls. iNPC treatment fully preserved visual acuity measured by optokinetic response. Electrophysiological recordings revealed that retina with the best iNPC-protected areas were 140-fold more sensitive to light stimulation than equivalent areas of contralateral eyes. The results described here support the therapeutic utility of iNPCs as autologous grafts for early-stage of AMD.

PMID: 25869002 [PubMed - as supplied by publisher]

J Vis Exp. 2015 Mar 8;(97).

Efficient derivation of retinal pigment epithelium cells from stem cells.

Westenskow P, Sedillo Z, Barnett A, Friedlander M.

Abstract: No cure has been discovered for age-related macular degeneration (AMD), the leading cause of vision loss in people over the age of 55. AMD is complex multifactorial disease with an unknown etiology, although it is largely thought to occur due to death or dysfunction of the retinal pigment epithelium (RPE), a monolayer of cells that underlies the retina and provides critical support for photoreceptors. RPE cell replacement strategies may hold great promise for providing therapeutic relief for a large subset of AMD patients, and RPE cells that strongly resemble primary human cells (hRPE) have been generated in

multiple independent labs, including our own. In addition, the uses for iPS-RPE are not limited to cell-based therapies, but also have been used to model RPE diseases. These types of studies may not only elucidate the molecular bases of the diseases, but also serve as invaluable tools for developing and testing novel drugs. We present here an optimized protocol for directed differentiation of RPE from stem cells. Adding nicotinamide and either Activin A or IDE-1, a small molecule that mimics its effects, at specific time points, greatly enhances the yield of RPE cells. Using this technique we can derive large numbers of low passage RPE in as early as three months.

PMID: 25867641 [PubMed - in process]

Ophthalmology. 2015 Apr 13. [Epub ahead of print]

Long-Term Results of Full Macular Translocation for Choroidal Neovascularization in Age-Related Macular Degeneration.

van Romunde SH, Polito A, Bertazzi L, Guerriero M, Pertile G.

PURPOSE: To investigate the long-term outcome of full macular translocation (FMT) for neovascular age-related macular degeneration (AMD) and to identify predictive factors.

DESIGN: Retrospective, uncontrolled case series.

PARTICIPANTS: Patients were considered for FMT if they had low vision in the fellow eye and choroidal neovascularization (CNV) along with (1) no response to vascular endothelial growth factor (VEGF) inhibitors, (2) retinal pigment epithelium (RPE) tear, (3) subretinal hemorrhage, (4) foveal scar tissue of recent onset, or (5) CNV before the availability of VEGF inhibitors. From 2004 through 2012, a total of 255 patients underwent FMT. Exclusion criteria were patients younger than 60 years, FMT for disease other than AMD, and a follow-up of less than 12 months.

METHODS: Preoperative, annual, and last distance best-corrected visual acuity (BCVA) were obtained retrospectively from patient files. Complications were recorded using funduscopy, optical coherence tomography, autofluorescence, and angiography.

MAIN OUTCOME MEASURES: Distance BCVA at 1 year and 5 years after surgery and at last visit compared with preoperative BCVA.

RESULTS: One hundred fifty-eight patients (mean follow-up, 45 months) were included. Median BCVA improved from 0.90 logarithm of the minimum angle of resolution (logMAR) before surgery to 0.70 logMAR 1 year after FMT (2 lines gained; $P = 0.000$). In a subgroup of 56 patients followed up for 5 years or more, median BCVA improved from 0.95 logMAR before surgery to 0.70 logMAR 1 year after surgery, and remained improved 5 years after FMT with a median BCVA of 0.80 logMAR (1.5 lines gained compared with preoperative BCVA; $P = 0.000$). The main complications were foveal RPE atrophy (n = 73; 47%) and CNV recurrence (n = 47; 30%). Foveal RPE atrophy (odds ratio [OR], 7.0), CNV recurrence (OR, 2.6), and proliferative vitreoretinopathy (PVR; OR, 17.6) were statistically significant predictors ($P < 0.05$) for losing 1 line or more at last visit.

CONCLUSIONS: In this study, BCVA was improved up to 5 years after FMT. Foveal RPE atrophy, CNV recurrence, and PVR carried a worse prognosis. In patients who are unlikely to benefit from VEGF inhibitors, FMT can be considered for second eyes with neovascular AMD.

PMID: 25881514 [PubMed - as supplied by publisher]

Pathogenesis

Immunol Rev. 2015 May;265(1):63-74.

Drivers of age-related inflammation and strategies for healthspan extension.

Goldberg EL, Dixit VD.

Abstract: Aging is the greatest risk factor for the development of chronic diseases such as arthritis, type 2 diabetes, cardiovascular disease, kidney disease, Alzheimer's disease, macular degeneration, frailty, and certain forms of cancers. It is widely regarded that chronic inflammation may be a common link in all these age-related diseases. This raises the question, can one alter the course of aging and potentially slow the development of all chronic diseases by manipulating the mechanisms that cause age-related inflammation? Emerging evidence suggests that pro-inflammatory cytokines interleukin-1 (IL-1) and IL-18 show an age-dependent regulation implicating inflammasome-mediated caspase-1 activation in the aging process. The Nod-like receptor (NLR) family of innate immune cell sensors, such as the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome controls the caspase-1 activation in myeloid-lineage cells in several organs during aging. The NLRP3 inflammasome is especially relevant to aging as it can get activated in response to structurally diverse damage-associated molecular patterns (DAMPs) such as extracellular ATP, excess glucose, ceramides, amyloids, urate, and cholesterol crystals, all of which increase with age. Interestingly, reduction in NLRP3-mediated inflammation prevents age-related insulin resistance, bone loss, cognitive decline, and frailty. NLRP3 is a major driver of age-related inflammation and therefore dietary or pharmacological approaches to lower aberrant inflammasome activation holds promise in reducing multiple chronic diseases of age and may enhance healthspan.

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Mol Vis. 2015 Apr 9;21:360-77. eCollection 2015.

Regulation of the hyperosmotic induction of aquaporin 5 and VEGF in retinal pigment epithelial cells: involvement of NFAT5.

Hollborn M, Vogler S, Reichenbach A, Wiedemann P, Bringmann A, Kohen L.

PURPOSE: High intake of dietary salt increases extracellular osmolarity, which results in hypertension, a risk factor of neovascular age-related macular degeneration. Neovascular retinal diseases are associated with edema. Various factors and channels, including vascular endothelial growth factor (VEGF) and aquaporins (AQPs), influence neovascularization and the development of edema. Therefore, we determined whether extracellular hyperosmolarity alters the expression of VEGF and AQPs in cultured human retinal pigment epithelial (RPE) cells.

METHODS: Human RPE cells obtained within 48 h of donor death were prepared and cultured. Hyperosmolarity was induced by the addition of 100 mM NaCl or sucrose to the culture medium. Alterations in gene expression and protein secretion were determined with real-time RT-PCR and ELISA, respectively. The levels of signaling proteins and nuclear factor of activated T cell 5 (NFAT5) were determined by western blotting. DNA binding of NFAT5 was determined with EMSA. NFAT5 was knocked down with siRNA.

RESULTS: Extracellular hyperosmolarity stimulated VEGF gene transcription and the secretion of VEGF protein. Hyperosmolarity also increased the gene expression of AQP5 and AQP8, induced the phosphorylation of p38 MAPK and ERK1/2, increased the expression of HIF-1α and NFAT5, and induced the DNA binding of NFAT5. The hyperosmotic expression of VEGF was dependent on the activation of p38 MAPK, ERK1/2, JNK, PI3K, HIF-1, and NFAT5. The hyperosmotic induction of AQP5 was in part dependent on the activation of p38 MAPK, ERK1/2, NF-κB, and NFAT5. Triamcinolone acetonide inhibited the hyperosmotic expression of VEGF but not AQP5. The expression of AQP5 was decreased by hypoosmolarity, serum, and hypoxia.

CONCLUSIONS: Hyperosmolarity induces the gene transcription of AQP5, AQP8, and VEGF, as well as the secretion of VEGF from RPE cells. The data suggest that high salt intake resulting in osmotic stress may aggravate neovascular retinal diseases and edema via the stimulation of VEGF production in RPE. The downregulation of AQP5 under hypoxic conditions may prevent the resolution of edema.

PMID: 25878490 [PubMed - in process] PMCID: PMC4390809

Mediators Inflamm. 2015;2015:673090. Epub 2015 Mar 22.

Contribution of Microglia-Mediated Neuroinflammation to Retinal Degenerative Diseases.

Madeira MH, Boia R, Santos PF, Ambrósio AF, Santiago AR.

Abstract: Retinal degenerative diseases are major causes of vision loss and blindness worldwide and are characterized by chronic and progressive neuronal loss. One common feature of retinal degenerative diseases and brain neurodegenerative diseases is chronic neuroinflammation. There is growing evidence that retinal microglia, as in the brain, become activated in the course of retinal degenerative diseases, having a pivotal role in the initiation and propagation of the neurodegenerative process. A better understanding of the events elicited and mediated by retinal microglia will contribute to the clarification of disease etiology and might open new avenues for potential therapeutic interventions. This review aims at giving an overview of the roles of microglia-mediated neuroinflammation in major retinal degenerative diseases like glaucoma, age-related macular degeneration, and diabetic retinopathy.

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Front Immunol. 2015 Mar 30;6:135. eCollection 2015.

Modulation of CD44 Activity by A6-Peptide.

Finlayson M.

Abstract: Hyaluronan (HA) is a non-sulfated glycosaminoglycan distributed throughout the extracellular matrix that plays a major role in cell adhesion, migration, and proliferation. CD44, a multifunctional cell surface glycoprotein, is a receptor for HA. In addition, CD44 is known to interact with other receptors and ligands, and to mediate a number of cellular functions as well as disease progression. Studies have shown that binding of HA to CD44 in cancer cells activates survival pathways resulting in cancer cell survival. This effect can be blocked by anti-CD44 monoclonal antibodies. A6 is a capped, eight l-amino acid peptide (Ac-KPSSPPEE-NH2) derived from the biologically active connecting peptide domain of the serine protease, human urokinase plasminogen activator (uPA). A6 neither binds to the uPA receptor (uPAR) nor interferes with uPA/uPAR binding. A6 binds to CD44 resulting in the inhibition of migration, invasion, and metastasis of tumor cells, and the modulation of CD44-mediated cell signaling. A6 has been shown to have no dose-limiting toxicity in animal studies. A6 has demonstrated efficacy and an excellent safety profile in Phase 1a, 1b, and 2 clinical trials. In animal models, A6 has also exhibited promising results for the treatment of diabetic retinopathy and wet age-related macular degeneration through the reduction of retinal vascular permeability and inhibition of choroidal neovascularization, respectively. Recently, A6 has been shown to be directly cytotoxic for B-lymphocytes obtained from patients with chronic lymphocytic leukemia expressing the kinase, ZAP-70. This review will discuss the activity of A6, A6 modulation of HA and CD44, and a novel strategy for therapeutic intervention in disease.

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Epidemiology

Ophthalmology. 2015 Apr 11. [Epub ahead of print]

A Population-Based Ultra-Widefield Digital Image Grading Study for Age-Related Macular Degeneration-Like Lesions at the Peripheral Retina.

Lengyel I, Csutak A, Florea D, Leung I, Bird AC, Jonasson F, Peto T.

PURPOSE: Our understanding of the relevance of peripheral retinal abnormalities to disease in general and in age-related macular degeneration (AMD) in particular is limited by the lack of detailed peripheral imaging studies. The purpose of this study was to develop image grading protocols suited to ultra-widefield imaging (UWFI) in an aged population.

DESIGN: A cross-sectional study of a random population sample in which UWFI was introduced at the 12-year review of the Reykjavik Eye Study in Iceland.

PARTICIPANTS: Five hundred seventy-six subjects 62 years of age or older.

METHODS: Ultra-widefield (up to 200°) color and autofluorescence images were obtained using the Optos P200CAF laser scanning ophthalmoscope (Optos plc, Dunfermline, Scotland). The images were graded at Moorfields Eye Hospital Reading Centre primarily based on the International Classification for AMD. Macular and peripheral changes were graded using a standardized grid developed for this imaging method.

MAIN OUTCOME MEASURES: Presence or absence of hard, crystalline, and soft drusen; retinal pigment epithelial changes; choroidal neovascularization (CNV); atrophy; and hypoautofluorescence and hyperautofluorescence were graded in the peripheral retina.

RESULTS: Of the eyes examined, 81.1% had AMD-like changes in the macula alone (13.6%), periphery alone (10.1%), and both periphery and macula (57.4%). There was no AMD-like CNV or pigment epithelial detachment in the periphery except in those cases in which these clearly originated from the macula. Seven patients had AMD-like atrophy in the periphery without end-stage disease in the macula. One patient with end-stage disease in the macula had normal periphery results on the color images. While analyzing the eyes, we detected pathologic appearances that were very reliably identified by graders.

CONCLUSIONS: Phenotyping the retinal periphery using the categories defined by the International Classification confirmed the presence of wide-ranging AMD-like pathologic changes even in those without central sight-threatening macular disease. Based on our observations, we propose here new, reliably identifiable grading categories that may be more suited for population-based UWFI.

PMID: 25870081 [PubMed - as supplied by publisher]

Neurodegener Dis. 2015 Apr 11. [Epub ahead of print]

The Relationship between Age-Related Macular Degeneration and Olfactory Function.

Kar T, Yildirim Y, Altundağ A, Sonmez M, Kaya A, Colakoglu K, Tekeli H, Cayonu M, Hummel T.

BACKGROUND: Olfactory dysfunction is a common symptom of many neurodegenerative diseases, and age-related macular degeneration (AMD) is a late-onset neurodegenerative disease.

OBJECTIVE: Thus, the aim of this study was to investigate olfactory functions in patients with AMD.

METHODS: A total of 69 subjects with AMD and 69 age- and sex-matched healthy controls were enrolled. After a complete ophthalmic evaluation, the AMD patients were subclassified as early- and late-stage AMD. Psychophysical testing of olfactory function was performed using the validated Sniffin' Sticks test.

RESULTS:

This study was carried out in 138 subjects, with a mean age of 74.3 ± 8.9 years (range 51-89). The current investigation showed the following two major findings: (1) patients with AMD had decreased olfactory abilities, especially in odor discrimination and odor identification, even at early stages compared to controls, whereas patients had decreased olfactory abilities in all subtasks of olfactory testings in advanced stages of AMD disease, and (2) as the visual acuity of AMD patients decreased, the olfactory abilities of these patients worsened.

CONCLUSION: This study demonstrated that AMD had significant negative effects on all orthonasal olfactory tasks, particularly in advanced stages. Similar to other neurodegenerative diseases, odor discrimination and identification seemed to be more affected than odor detection threshold tasks.

PMID: 25871947 [PubMed - as supplied by publisher]

Genetics

BMC Ophthalmol. 2015 Mar 6;15(1):18.

Common synonymous variants in ABCA4 are protective for chloroquine induced maculopathy (toxic maculopathy).

Grassmann F, Bergholz R, Mändl J, Jägle H, Ruether K, Weber BH.

BACKGROUND: Chloroquine (CQ) and hydroxychloroquine (HCQ) are used to treat auto-immune related diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus. Both drugs however can cause retinal toxicity eventually leading to irreversible maculopathy and retinopathy. Established risk factors are duration and dosage of treatment while the involvement of genetic factors contributing to toxic maculopathy is largely unclear. To address the latter issue, this study aimed to expand on earlier efforts by (1) evaluating risk-altering variants known to be associated with age-related macular degeneration (AMD), a frequent maculopathy in individuals over 55 years of age, and (2) determining the contribution of genetic variants in the coding sequence of the ABCA4 gene.

METHODS: The ABCA4 gene was analyzed by deep sequencing technology using a personal genome machine (Ion Torrent) with 200 bp read length. Assessment of AMD variants was done by restriction enzyme digestion of PCR products and TaqMan SNP genotyping. Effect sizes, p-values and confidence intervals of common variants were evaluated by logistic regression (Firth's bias corrected). To account for multiple testing, p-values were adjusted according to the false discovery rate.

RESULTS: We found no effects of known AMD-associated variants on the risk of toxic maculopathy. In contrast, we report a statistically significant association of common variants in the ABCA4 gene with retinal disease, assessed by a score-based variance-component test (PSKAT = 0.0055). This association remained significant after adjustment for environmental factors like age and duration of medication and was driven by three common variants in ABCA4 (c.5682G > C, c.5814A > G, c.5844A > G), all conferring a reduced risk for toxic maculopathy.

CONCLUSIONS: Our findings demonstrate that minor alleles of common genetic variants in ABCA4 significantly reduce susceptibility to develop toxic maculopathy under CQ treatment. A refined risk profile based on genetic and environmental factors may have implications for revised recommendations in CQ as well as HCQ treatment.

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J Ophthalmol. 2015;2015:821918. Epub 2015 Mar 25.

Joint Effect of CFH and ARMS2/HTRA1 Polymorphisms on Neovascular Age-Related Macular Degeneration in Chinese Population.

Fang K, Gao P, Tian J, Qin X, Yu W, Li J, Chen Q, Huang L, Chen D, Hu Y, Li X.

Purpose: The etiology of neovascular age-related macular degeneration (nAMD) cannot be completely explained by identified environmental risk factors or single-locus gene variants. This study was to explore the potential interactions among gene variants on nAMD in Chinese population.

Methods. 43 SNPs located in different genes were genotyped in 932 Chinese individuals (464 nAMD patients and 468 controls). We explored the potential interactions among gene variants using generalized multifactor dimensionality reduction (GMDR) algorithm and the method to measure the departure from the additivity model.

Results: The joint effect that involved CFH rs1061170 and HTRA1 rs3793917 was shown statistically significant ($P < 0.001$) with the highest cross-validation consistency (10/10) and the best testing balanced accuracy (64.50%). In addition, based on the method to measure the departure from the additivity model, the synergy index (S) was 2.63 (1.09-6.38) and the attributable proportion due to interaction (AP) was 55.7% (21.4%-89.9%), which suggested that a common pathway may exist for these genes for nAMD. Those who carried CC for rs3793917 and TC/CC for rs1061170 were at the highest risk of nAMD (OR: 9.76, 95% CI: 4.65-20.51).

Conclusions: Evidence that the joint effect that involved CFH and ARMS2/HTRA1 may contribute to the risk of neovascular AMD in Chinese population was obtained.

PMID: 25883802 [PubMed] PMCID: PMC4389821

Graefes Arch Clin Exp Ophthalmol. 2015 Jan 21. [Epub ahead of print]

Combined silencing of TGF-β2 and Snail genes inhibit epithelial-mesenchymal transition of retinal pigment epithelial cells under hypoxia.

Feng Z, Li R, Shi H, Bi W, Hou W, Zhang X.

BACKGROUND: The formation of scar-like fibrous tissue in age-related macular degeneration (AMD) is associated with hypoxia. Under hypoxia, retinal pigment epithelial (RPE) cells can secret more transforming growth factor-β2 (TGF-β2), which is determined to induce epithelial-mesenchymal transition (EMT) at certain concentrations. Whether hypoxia can induce EMT by stimulating RPE cell line secrets TGF-β2 or not remains unknown. To gain a better understanding of the signaling mechanisms of fibrosis in AMD under hypoxic conditions, we investigated EMT in retinal pigment epithelial (RPE) cells and the effect of TGF-β2 and Snail in this process.

METHODS: Human RPE cell line (ARPE-19) was incubated with 5 % O2 for different periods of time. The expression of N-cadherin, α-smooth muscle actin (α-SMA), TGF-β2 , and Snail were determined by Western blot and real-time PCR. Cell proliferation was assessed by CCK8 kit. RNA interference was used for multi-gene silencing of TGF-β2 and Snail genes.

RESULTS: N-cadherin was decreased and mesenchymal cell marker α-SMA was increased after the ARPE -19 cell line was incubated with 5 % O2. Meanwhile, the proliferation capability of the cell line was increased. TGF-β2 and Snail expression were increased in a time-dependent manner under hypoxia. After multi-silencing TGF-β2 and Snail genes, N-cadherin was increased and α-SMA was reduced. Meanwhile, the proliferation of the cell line was suppressed.

CONCLUSIONS: Under hypoxic conditions, RPE cells undergo EMT. Endogenic TGF-β2 and Snail are involved in this process. Furthermore, knockdown of both TGF-β2 and Snail inhibited EMT to a greater

extent than knockdown of either gene individually.

PMID: 25875044 [PubMed - as supplied by publisher]

Nat Commun. 2015 Apr 15;6:6687.

Whole-exome sequencing implicates UBE3D in age-related macular degeneration in East Asian populations.

Huang LZ, Li YJ, Xie XF, et al.

Abstract: Age-related macular degeneration (AMD) is a leading cause of irreversible central blindness among the elderly worldwide. We use exome sequencing to analyse nonsynonymous single-nucleotide variants (SNVs) across the whole genome of 216 neovascular AMD cases and 1,553 controls. As a follow-up validation, we evaluate 3,772 neovascular AMD cases and 6,942 controls from five independent cohorts in the East Asian population. Here we show strong evidence of an association at a novel, missense SNV, rs7739323, which is located in the ubiquitin protein ligase E3D (UBE3D) gene (Pmeta=1.46 × 10(-9), odds ratio (OR)=0.74, 95% confidence interval (CI): 0.63-0.88). Furthermore, ablation of the UBE3D protein lead to an abnormal amount of pigment granules deposited in retinal pigment epithelium microvilli area and an abnormal response on electroretinography (ERG) in UBE3D(+/-) heterozygous mice. Our findings indicate that the ubiquitin-proteasome system may play a role in the pathogenesis of neovascular AMD.

PMID: 25872646 [PubMed - in process]

Genet Mol Res. 2015 Mar 13;14(1):1855-67.

Gene expression profiles of primary retinal pigment epithelial cells from apolipoprotein E knockout and human apolipoprotein E2 transgenic mice.

Jo DH, Lee JH, Jun HJ, Kim J, Wen Q, Hoang MH, Yu YS, Kim JH, Lee SJ.

Abstract: Age-related macular degeneration (AMD) causes visual impairment in the elderly. In non-neovascular AMD, studies involving human subjects have suggested potential involvement of aberrant lipid metabolism. However, there have been no reports on gene expression patterns in animal models of non-neovascular AMD with abnormal lipid metabolism such as apolipoprotein E knockout and human apolipoprotein E2 transgenic mice. Transcriptome analysis was performed using retinal pigment epithelium cells of apoE knockout and apolipoprotein E2 mice using microarray analysis. C57BL/6, Rxrb, Pparbp, Vldlr, and Edf1, which are primarily related to lipid metabolism, were upregulated, while Tgfbr1 and Pdgfb, which are related to pathologic angiogenesis in AMD, were downregulated in both types of mice. Apolipoprotein E knockout and apolipoprotein E2 mice showed characteristic gene expression patterns in the transcriptome analysis of primary retinal pigment epithelium cells. These results suggest that specific genes associated with lipid metabolism and angiogenesis are involved in the pathogenesis and progression of AMD.

PMID: 25867331 [PubMed - in process]

JAMA Ophthalmol. 2015 Apr 16. doi: 10.1001/jamaophthalmol.2015.0814. [Epub ahead of print]

Phenotypic Characterization of Complement Factor H R1210C Rare Genetic Variant in Age-Related Macular Degeneration.

Ferrara D, Seddon JM.

Importance: The complement factor H R1210C rare variant confers the strongest genetic risk for age-related macular degeneration and earlier age at onset; however, its associated phenotype has not been

well characterized.

Objective: To describe specific fundus features of a white population with the R1210C rare variant.

Design, Setting, and Participants: Fundus features specific for diagnosis and disease staging were retrospectively characterized by systematic review of all available fundus images for each patient, including color photography, fluorescein angiography, fundus autofluorescence, and optical coherence tomography, at a tertiary ophthalmologic referral center. For this retrospective observational study conducted from 2012 to 2014, enrolled patients with the variant and their family members without the variant were identified from the Age-Related Macular Degeneration Study for a family-based study arm. For patients with the variant but without a family member enrolled in the study, age-matched comparison individuals without the variant were selected randomly from the database.

Main Outcomes and Measures: The presence of drusen in the macula (macular drusen score) and estimated number (total macular drusen score) were assessed. The presence of drusen in the extramacular regions (extramacular drusen score), pigmentary abnormalities, and disease staging were also evaluated. Binary logistic regression models were used to evaluate the association between rare variant status and ocular phenotypes.

Results: Images from a total of 143 patients (283 eyes), including 62 patients with the rare variant, were analyzed. Drusen score covariates were associated with the R1210C rare variant. A larger proportion of patients carrying the variant had the highest level of macular and total macular drusen scores compared with those without the variant (57.9% vs 16.7% and 52.9% vs 14.2%, respectively; P for trend < .001 for both scores). Patients carrying the rare variant had a much greater likelihood of having advanced disease (odds ratio, 7.0; 95% CI, 3.1-16.2; P < .001). A higher prevalence of geographic atrophy was observed among patients carrying the variant (odds ratio, 13.7; 95% CI, 5.0-37.7; P < .001).

Conclusions and Relevance: The typical phenotype of the complement factor H R1210C rare variant is associated with extensive drusen accumulation in the macula and throughout the fundus, as well as with a high risk for having advanced disease. Better characterization of genetic profiles in age-related macular degeneration may be important for screening and future therapeutic strategies for this vision-threatening condition.

PMID: 25880396 [PubMed - as supplied by publisher]

Diet, lifestyle & low vision

PLoS One. 2015 Apr 17;10(4):e0124533. eCollection 2015.

The self-reported clinical practice behaviors of Australian optometrists as related to smoking, diet and nutritional supplementation.

Downie LE, Keller PR.

OBJECTIVE: The primary aim of this study was to examine the self-reported, routine clinical practice behaviors of Australian optometrists with respect to advice regarding smoking, diet and nutritional supplementation. The study also sought to assess the potential influence of practitioner age, gender, practice location (major city versus regional), therapeutic-endorsement status and personal nutritional supplementation habits upon management practices in these areas.

METHODS: A survey was electronically distributed to Australian optometrists (n = 4,242). Respondents anonymously provided information about their personal demographics and lifestyle behaviors (i.e., age, gender, practice location, therapeutic-endorsement status, smoking status, nutritional supplement intake) and routine patient management practices with respect to advice across three domains: smoking, diet and nutritional supplementation. Multivariate logistic regression analyses were performed to assess for potential

effects of the listed factors on practitioner behavior.

RESULTS: A total of 283 completed surveys were received (completed survey response rate: 6.7%). Fewer than half of respondents indicated routinely asking their patients about smoking status. Younger practitioners were significantly ($p < 0.05$) less likely to enquire about patients' smoking behaviors, but this did not extend to counseling for smoking cessation. Almost two-thirds of respondents indicated routinely counseling patients about diet. About half of practitioners specified routinely asking their patients about nutritional supplement intake; this form of questioning was significantly more likely if the respondent was female ($p < 0.05$). Practitioners who recommended nutritional supplements most commonly did so for age-related macular degeneration (91.2%) and dry eye disease (63.9%). The primary source of evidence used to guide practitioners' nutrition-related patient management was reported to be peer-reviewed publications.

CONCLUSIONS: These findings demonstrate that there are no clear predictors of practitioner behavior across the three domains. Overall, this study suggests that there is scope for Australian optometrists to improve their routine engagement by questioning patients, as well as providing evidence-based clinical advice, about smoking status, diet and nutritional supplement behaviors, being key modifiable lifestyle risk factors with long-term implications for eye health.

PMID: 25886641 [PubMed - in process]

Crit Rev Food Sci Nutr. 2015 Apr 15:0. [Epub ahead of print]

Efficacy and Safety of Saffron Supplementation: Current Clinical Findings.

Broadhead GK, Chang A, Grigg J, McCluskey P.

Abstract: Saffron (Crocus savitus) is a Middle-Eastern herb with strong antioxidant properties. Its major constituents, safranal, crocin and crocetin, are also antioxidants and bear structural similarities to other well known natural antixodant substances, such as zeaxanthin. Given the role of oxidative stress in many diseases, considerable interest has been shown into the potential role of saffron supplementation as a treatment for a range of diseases. In vitro and animal studies have provided evidence that saffron and its constituents may be potent therapies for a range of pathologies, including Alzheimer's disease, age-related macular degeneration and cardiac ischaemia. Whether these findings translate into clinical efficacy, however, has as of yet been incompletely assessed. This makes assessing the role of saffron supplementation in these diseases difficult. Here, we review the current human clinical evidence supporting saffron supplementation as a treatment for a range of pathologies and the underlying science supporting its use.

PMID: 25875654 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2015 Mar 3;15(1):16.

Baseline traits of patients presenting at a low vision clinic in Shanghai, China.

Gao G, Ouyang C, Dai J, Xue F, Wang X, Zou L, Chen M, Ma F, Yu M.

BACKGROUND: Low vision, along with cataract, trachoma, onchocerciasis, childhood blindness and refractive error, is one of the priorities in the global initiative, VISION 2020-The Right to Sight. The purpose of this study was to characterize the traits of patients presenting at a low vision clinic in China.

METHODS: A retrospective study was conducted of the records of 299 patients who visited the Low Vision Clinic of Eye and ENT Hospital Affiliated to Fudan University from January 2009 to May 2014. Reviewed parameters included age, gender, education, occupation, cause of visual impairment and types of low vision aids (LVAs) dispensed.

RESULTS: Of all the patients (193 male; aged from 3 to 96 years, with a mean of 29.74 ± 25.23 years), 43.48% experienced moderate visual impairment, 25.42% had severe visual impairment and 21.07% were blind. The four major causes of visual impairment were congenital cataract (14.38%), degenerative myopia (13.71%), juvenile macular degeneration (9.36%) and retinitis pigmentosa (9.36%). The most common causes of visual impairment were congenital cataract (22.67%) in 0-19-year-olds, retinitis pigmentosa (20.62%) in 20-59-year-olds, and age-related macular degeneration (36.54%) in the 60+ group. With the help of LVAs, a significant improvement of distance and/or near vision or visual field was observed in 243 patients, of whom 185 accepted LVAs and 58 patients refused due to high price, inconvenience, young age (≤6 y), clumsy appearance and ignorance. The most commonly dispensed LVAs were stand magnifiers (21.57%) followed by spectacle-type LVAs (19.21%).

CONCLUSIONS: The majority of the patients in our low vision clinic were young, the main causes of visual impairment were congenital and hereditary diseases. Stand magnifiers were the most commonly dispensed LVAs. High price was the major reason for refusing LVAs.

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