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Drug treatment

Eye (Lond). 2015 May 29. [Epub ahead of print]

Transitioning to intravitreal aflibercept following a previous treat-and-extend dosing regimen in neovascular age-related macular degeneration: 24-month results.

Homer N, Grewal DS, Mirza RG, Lyon AT, Gill MK.

PURPOSE: To evaluate frequency of injections, visual and anatomical outcomes of neovascular age-related macular degeneration (nAMD) patients transitioned to intravitreal aflibercept after failure to extend treatment interval beyond 8 weeks with prior intravitreal bevacizumab or ranibizumab.

METHODS: Retrospective review of patients with nAMD switched to aflibercept following ≥ 6 prior intravitreal ranibizumab or bevacizumab injections at 4-8-week intervals. Three monthly aflibercept injections were given followed by a treat-and-extend dosing regimen.

RESULTS: Twenty-one eyes of 18 patients who had received a mean of 23.8 ± 18.8 (mean $\pm$ SD; range 6-62) prior ranibizumab or bevacizumab injections were included. Over a mean follow-up of 24 months after the transition, 9.2 ± 2.9 (range 4-21) aflibercept injections were required. Interval between aflibercept injections increased to 57.3 days (range 35-133 days), as compared with 37 ± 6.1 days (range 29-54 days) with the prior agents ($P=0.01$). Mean best-corrected visual acuity was preserved (0.42 ± 0.31 vs 0.42 ± 0.23 logMAR; $P=0.2$). Mean OCT central subfoveal thickness (292.1 ± 83.2 μ m to 283.6 ± 78.6 μ m; $P=0.4$) and mean macular volume (7.9 ± 0.95 mm³ to 7.67 ± 0.94 mm³; $P=0.16$) remained stable.

CONCLUSION: Patients requiring treatment more frequently than every 8 weeks with ranibizumab and bevacizumab were transitioned to >8 -week treatment interval with aflibercept while maintaining the anatomic and visual gains. Eye advance online publication, 29 May 2015; doi:10.1038/eye.2015.87.

PMID: 26021870 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 May 1;56(5):3279-86.

Systemic counterregulatory response of placental growth factor levels to intravitreal aflibercept therapy.

Zehetner C, Bechrakis NE, Stattin M, Kirchmair R, Ulmer H, Kralinger MT, Kieselbach GF.

PURPOSE: Placental growth factor (PlGF) has been implicated as a contributor to resistance against anti-VEGF therapy. The purpose of the present study was to analyze the systemic levels of PlGF, VEGF-A, and VEGF-B in patients with neovascular age-related macular degeneration (AMD) after treatment with aflibercept, ranibizumab, or bevacizumab.

METHODS: Totals of 19 patients were treated with intravitreal aflibercept, 19 with ranibizumab, and 18 with bevacizumab. The cytokine levels were measured by ELISA just before the injection, and 7 days and 1 month thereafter. Age- and sex-matched participants (n = 22) served as controls.

RESULTS: The median PIGF plasma concentration at baseline was <12.0 pg/mL in the control group as well as in all three anti-VEGF treatment cohorts. After intravitreal aflibercept injection, a significant upregulation of systemic PIGF could be observed in all treated patients (38.0 [31.0-44.0] pg/mL after 1 week [P < 0.001] and 16.0 [0.0-19.0] pg/mL [P = 0.005] after 4 weeks). No significant effects on plasma PIGF concentrations could be detected in those treated with ranibizumab and bevacizumab. The systemic VEGF-A levels were significantly reduced 1 and 4 weeks after intravitreal aflibercept (P < 0.001, P < 0.001) and bevacizumab (P < 0.001, P < 0.01) injections. No significant effects on plasma cytokine concentrations could be observed in the ranibizumab cohort. No significant effects on systemic VEGF-B could be observed in any of the treatment groups.

CONCLUSIONS: In this study, we report a significant systemic upregulation of the proangiogenic cytokine PIGF after intravitreal administration of aflibercept. This might represent a counter-regulatory response to antiangiogenic therapy.

PMID: 26024110 [PubMed - in process]

Eur J Pharm Biopharm. 2015 May 25. pii: S0939-6411(15)00219-2. [Epub ahead of print]

Nanoengineering of Therapeutics for Retinal Vascular Disease.

Gahlaut N, Suarez S, Uddin MI, Gordon AY, Evans SM, Jayagopal A.

Abstract: Retinal vascular diseases, including diabetic retinopathy, neovascular age related macular degeneration, and retinal vein occlusion, are leading causes of blindness in the Western world. These diseases share several common disease mechanisms, including vascular endothelial growth factor (VEGF) signaling, hypoxia, and inflammation, which provide opportunities for common therapeutic strategies. Treatment of these diseases using laser therapy, anti-VEGF injections, and/or steroids has significantly improved clinical outcomes. However, these strategies do not address the underlying root causes of pathology, and may have deleterious side effects. Furthermore, many patients continue to progress toward legal blindness despite receiving regular therapy. Nanomedicine, the engineering of therapeutics at the 1-100 nm scale, is a promising approach for improving clinical management of retinal vascular diseases. Nanomedicine-based technologies have the potential to revolutionize the treatment of ophthalmology, through enabling sustained release of drugs over several months, reducing side effects due to specific targeting of dysfunctional cells, and interfacing with currently "undruggable" targets. We will discuss emerging nanomedicine-based applications for treatment of complications associated with retinal vascular diseases, including angiogenesis and inflammation.

PMID: 26022642 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2015 May 28. [Epub ahead of print]

Intraocular and systemic inflammation-related cytokines during one year of ranibizumab treatment for neovascular age-related macular degeneration.

Fauser S, Viebahn U, Muether PS.

PURPOSE: To determine inflammation-related intraocular and systemic cytokine concentrations in neovascular age-related macular degeneration (nAMD) compared with controls and to assess the influence of long-term intravitreal ranibizumab treatment over 1 year.

METHODS: Aqueous humour and blood plasma of 21 controls and 17 treatment-naive nAMD patients were

collected prior to cataract surgery or ranibizumab treatment. Follow-up specimens in nAMD patients were acquired immediately prior to subsequent ranibizumab injections as needed. Multiplex bead assays were conducted for ten inflammation-related cytokines and vascular endothelial growth factor (VEGF). p-values were Holm-Bonferroni-corrected for multiple comparisons.

RESULTS: Prior to ranibizumab treatment, initiation aqueous humour levels of monocyte chemo-attractant protein (MCP)-1/CCL2 ($p = 0.005$) and vascular cell adhesion molecule (VCAM) ($p = 0.002$) were elevated in nAMD compared with controls. Other intraocular cytokines did not differ, including VEGF. In plasma, no differences between nAMD patients and controls were found at baseline. Pro re nata ranibizumab treatment over 12 months with 8 ± 2 injections reduced aqueous VEGF ($p < 0.0001$) with a trend to reduced VEGF plasma concentrations ($p = 0.046$), with all specimens taken at least 28 days after the previous injection. All other local and systemic cytokines remained unchanged.

CONCLUSION: Neovascular age-related macular degeneration is associated with local ocular MCP-1/CCL2 and VCAM elevations, suggesting a local inflammatory involvement in the pathophysiology of nAMD. We did not detect systemic differences. Ranibizumab treatment does not result in local or systemic changes of these cytokines, in contrast to VEGF suppression. MCP-1/CCL2 and VCAM may be potential additional treatment targets for nAMD.

PMID: 26016605 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2015 May 22. [Epub ahead of print]

Dexamethasone intravitreal implants for diabetic macular edema refractory to ranibizumab monotherapy or combination therapy.

Gutiérrez-Benítez L, Millan E, Arias L, Garcia P, Cobos E, Caminal M.

OBJECTIVE: To determine the effectiveness and local safety of dexamethasone intravitreal implants as a treatment in diabetic macular edema (DME) refractory to intravitreal injections of ranibizumab monotherapy or combination therapy.

METHODS: A retrospective study conducted on patients with DME refractory to ranibizumab monotherapy or combined with other treatments treated with dexamethasone intravitreal implants. The parameters analyzed were visual acuity (VA) by ETDRS (Early Treatment Diabetic Retinopathy Study) charts and foveal thickness by spectral-domain optical coherence tomography (SD-OCT) before the treatment, 2 months after treatment, and at the end of the follow-up.

RESULTS: A total of 14 eyes of 14 patients were included, with a mean age of 64 years (SD: 9.5; range 41-78) and a mean follow-up of 7.6 months. The mean VA improved from 53 letters to 59 letters at 2 months ($P=.03$), and 57 at the end of the follow-up period ($P=.3$). The mean foveal thickness decreased from 502 μ to 304 μ at 2 months ($P=.001$), and 376 μ at the end of the follow-up period ($P=.009$). Further treatment with intravitreal dexamethasone was required in 43% of the patients, and 21% had increased intraocular pressure, which was controlled with topical medication.

CONCLUSIONS: Intravitreal dexamethasone implant is an effective and locally safe treatment for the management of DME refractory to ranibizumab monotherapy or combined with other treatments.

PMID: 26008920 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Jun;122(6):e37-8.

Re: Korobelnik et al.: Intravitreal aflibercept for diabetic macular edema

Hashmonay R, Parikh S.

PMID: 26008915 [PubMed - in process]

Washington (DC): National Academies Press (US); 2015 Jan.

Advancing Therapeutic Development for Dry Age-Related Macular Degeneration (AMD): Workshop in Brief.

Editors, Institute of Medicine.

The National Academies Collection: Reports funded by National Institutes of Health.

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Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2015 May 1;56(5):3187-95.

Toward a specific classification of polypoidal choroidal vasculopathy: idiopathic disease or subtype of age-related macular degeneration.

Coscas G, Lupidi M, Coscas F, Benjelloun F, Zerbib J, Dirani A, Semoun O, Souied EH.

PURPOSE: To suggest a clinical distinction between idiopathic polypoidal choroidal vasculopathy (PCV) and secondary polyps associated with neovascular age-related macular degeneration (NV-AMD).

METHODS: The study was a retrospective case series of 52 eyes of 52 consecutive patients (31 females and 21 males) diagnosed with PCV. Initial diagnosis was based on scanning laser ophthalmoscope-indocyanine green angiography (SLO-ICGA) in association with fluorescein angiography (FA) and optical coherence tomography (OCT). All the data and images were analyzed in a masked fashion by four experienced examiners in two different sessions: the first, to classify patients into the two hypothesized groups (idiopathic polyps or NV-AMD-related polyps); the second, following a predetermined scheme, to describe objective features. The results obtained in each session underwent a cross multivariate analysis to identify statistically significant differences ($P \leq 0.05$) between the two groups.

RESULTS: The two groups were clinically different on the basis of FA (leakage origin [$P = 0.001$] and presence of drusen [$P = 0.001$]), ICGA (evidence of choroidal neovascularization [CNV; $P = 0.001$] and/or branching vascular network [BVN; $P = 0.001$]), OCT imaging (type of pigmented epithelium detachment [$P = 0.001$], presence of BVN [$P = 0.001$], and subfoveal choroidal thickness [$P = 0.001$]). Further significant differences were observed according to the location of lesion (uni- or multifocal) ($P = 0.001$), type of CNV ($P = 0.001$), and best-corrected visual acuity ($P = 0.001$).

CONCLUSIONS: Our study demonstrated clinical and statistically significant differences between idiopathic PCV and NV-AMD-related polyps that could be considered as distinct entities. Although they share some similarities, mainly the sub-RPE location, the ability to identify a specific clinical pattern suggests a more specific therapeutic approach for these two entities.

PMID: 26024102 [PubMed - in process]

Eye (Lond). 2015 May 29. [Epub ahead of print]

Ganglion cell complex thickness in nonexudative age-related macular degeneration.

Yenice E, Şengün A, Soyugelen Demirok G, Turaçlı E.

Purpose: To evaluate ganglion cell complex (GCC) thickness with spectral domain optical coherence tomography (SD-OCT) in eyes with nonexudative age-related macular degeneration (NEAMD).

Methods: Forty-seven eyes of 28 patients with nonexudative age-related macular degeneration (NEAMD) and 54 eyes of 28 age-matched healthy subjects were enrolled. Each subject underwent a complete ophthalmic examination before SD-OCT were obtained. Macular scans were taken with software version 6.0 of the ganglion cell analysis (GCA) algorithm. GCC thickness was evaluated automatically as the average, minimum, temporal superior, superior, nasal superior, nasal inferior, inferior, and temporal-inferior segments by SD-OCT and parameters were compared between groups.

Results: The mean age was 68.7 ± 8.73 years in patient group, and 61.51 ± 5.66 years in control group. There were no significant differences in mean age, gender distribution, intraocular pressure, and spheric equivalent at imaging between the groups ($P > 0.05$). The mean ($\pm$ SD) GCC thicknesses were as follows; average 71.53 ± 16.53 μ m, minimum 62.36 ± 21.51 μ m, temporal superior 72.23 ± 14.60 μ m, superior 72.76 ± 20.40 μ m, nasal superior 72.31 ± 20.13 μ m, nasal inferior 69.74 ± 20.51 μ m, inferior 69.38 ± 19.03 μ m, and temporal-inferior 73.12 ± 15.44 μ m in patient group. Corresponding values in control group were 81.46 ± 4.90 μ m, 78.66 ± 6.00 μ m, 81.51 ± 4.66 μ m, 82.94 ± 5.14 μ m, 81.79 ± 5.86 μ m, 80.94 ± 6.18 μ m, 80.14 ± 6.30 μ m, and 81.75 ± 5.26 μ m, respectively. There were significant differences between two groups in each segments (Mann-Whitney U-test, $P < 0.05$).

Conclusion: The average GCC thickness values (in all segments) of NEAMD patients were lower than control group. NEAMD, which is considered as a disease of outer layers of retina, may be accompanied with a decrease of ganglion cell thickness, so inner layers of retina may be affected. Eye advance online publication, 29 May 2015; doi:10.1038/eye.2015.86.

PMID: 26021868 [PubMed - as supplied by publisher]

Chin Med J (Engl). 2015 5th Jun;128(11):1516-1522.

Correlation of In Vivo and In Vitro Methods in Measuring Choroidal Vascularization Volumes Using a Subretinal Injection Induced Choroidal Neovascularization Model.

Nie C, Zhang MN, Zhao HW, Olsen TD, Jackman K, Hu LN, Ma WP, Chen XF, Wang J, Zhang Y, Gao TS, Uehara H, Ambati BK, Luo L.

BACKGROUND: In vivo quantification of choroidal neovascularization (CNV) based on noninvasive optical coherence tomography (OCT) examination and in vitro choroidal flatmount immunohistochemistry stained of CNV currently were used to evaluate the process and severity of age-related macular degeneration (AMD) both in human and animal studies. This study aimed to investigate the correlation between these two methods in murine CNV models induced by subretinal injection.

METHODS: CNV was developed in 20 C57BL6/j mice by subretinal injection of adeno-associated viral delivery of a short hairpin RNA targeting sFLT-1 (AAV.shRNA.sFLT-1), as reported previously. After 4

weeks, CNV was imaged by OCT and fluorescence angiography. The scaling factors for each dimension, x, y, and z ($\mu\text{m}/\text{pixel}$) were recorded, and the corneal curvature standard was adjusted from human (7.7) to mice (1.4). The volume of each OCT image stack was calculated and then normalized by multiplying the number of voxels by the scaling factors for each dimension in Seg3D software (University of Utah Scientific Computing and Imaging Institute, available at <http://www.sci.utah.edu/cibc-software/seg3d.html>). Eighteen mice were prepared for choroidal flatmounts and stained by CD31. The CNV volumes were calculated using scanning laser confocal microscopy after immunohistochemistry staining. Two mice were stained by Hematoxylin and Eosin for observing the CNV morphology.

RESULTS: The CNV volume calculated using OCT was, on average, 2.6 times larger than the volume calculated using the laser confocal microscopy. The correlation statistical analysis showed OCT measuring of CNV correlated significantly with the in vitro method ($R^2 = 0.448$, $P = 0.001$, $n = 18$). The correlation coefficient for CNV quantification using OCT and confocal microscopy was 0.693 ($n = 18$, $P = 0.001$).

CONCLUSIONS: There is a fair linear correlation on CNV volumes between in vivo and in vitro methods in CNV models induced by subretinal injection. The result might provide a useful evaluation of CNV both for the studies using CNV models induced by subretinal injection and human AMD studies.

PMID: 26021510 [PubMed - as supplied by publisher]

Nihon Rinsho Meneki Gakkai Kaishi. 2015;38(2):79-85.

Retinal regeneration with iPS cells - Clinical trials for retinal degenerative disorders.

Sugita S.

Abstract: Potential for re-programming cells has become widely accepted as a tool for obtaining transplantation materials. There has been great interest in cell-based therapies, including retinal transplants, because there is a reduced risk of immune rejection. Stem cells have the capacity for self-renewal plus the capacity to generate several differentiated cells. They are derived from many sources including human adult-derived induced pluripotent stem (iPS) cells and have found early application in the context of ocular disease. In results, our established iPS-retinal pigment epithelial (RPE) cells are high-quality RPE cells. iPS cells-derived RPE cells clearly showed polygonal morphology (mostly hexagonal) and contained melanin. Moreover, RPE cells derived from iPS cells had many characteristics of mature RPE cells in vivo, but no characteristics of pluripotent stem cells. Recently, we transplanted RPE cell sheets to treat a patient with wet age-related macular degeneration (September, 2014). In addition, we are now conducting experiments to determine whether allogeneic T cells can recognize iPS-RPE cells from HLA-A, B, DRB1 locus homozygote donors. iPS bank might be useful as allografts in retinal disorders, if the recipient T cells cannot respond to allogeneic RPE cells because of match to some of main HLA antigens.

PMID: 26016634 [PubMed - in process]

Aging Clin Exp Res. 2015 May 24. [Epub ahead of print]

Systemic endothelial function in cases with wet-type age-related macular degeneration.

Arifoglu HB, Karatepe Hashas AS, Atas M, Sarli B, Ozkose A, Demircan S.

BACKGROUND: Choroidal endothelial dysfunction plays key role in wet-type age-related macular degeneration (AMD). Peripheral vascular endothelial function is not known in wet AMD.

OBJECTIVE: We aimed to analyze peripheral vascular endothelial function in cases with wet-type age-related macular degeneration by measuring flow-mediated dilatation (FMD).

MATERIALS AND METHODS: The study included 20 cases with wet AMD (Group 1, mean age 65.9 ± 7.2 years) and 24 healthy individuals (Group 2, mean age 62.0 ± 11.9 years). In all cases, a cardiologist

assessed the responses of endothelial function by measuring the FMD following brachial artery occlusion.

RESULTS: Mean FMD, an indicator of endothelial function was found to be 6.4 ± 2.7 % in Group 1 and 15.6 ± 7.3 % in Group 2 ($p < 0.001$). There was no significant difference between patient and control groups regarding age, sex, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, ESR and CRP.

CONCLUSION: Reduced FMD is present in patients with wet AMD, suggesting that impaired peripheral endothelial function may be involved in its pathogenesis.

PMID: 26003670 [PubMed - as supplied by publisher]

PLoS One. 2015 May 29;10(5):e0128418.

A Quantitative and Standardized Method for the Evaluation of Choroidal Neovascularization Using MICRON III Fluorescein Angiograms in Rats.

Wigg JP, Zhang H, Yang D.

INTRODUCTION: In-vivo imaging of choroidal neovascularization (CNV) has been increasingly recognized as a valuable tool in the investigation of age-related macular degeneration (AMD) in both clinical and basic research applications. Arguably the most widely utilised model replicating AMD is laser generated CNV by rupture of Bruch's membrane in rodents. Heretofore CNV evaluation via in-vivo imaging techniques has been hamstrung by a lack of appropriate rodent fundus camera and a non-standardised analysis method. The aim of this study was to establish a simple, quantifiable method of fluorescein fundus angiogram (FFA) image analysis for CNV lesions.

METHODS: Laser was applied to 32 Brown Norway Rats; FFA images were taken using a rodent specific fundus camera (Micron III, Phoenix Laboratories) over 3 weeks and compared to conventional ex-vivo CNV assessment. FFA images acquired with fluorescein administered by intraperitoneal injection and intravenous injection were compared and shown to greatly influence lesion properties. Utilising commonly used software packages, FFA images were assessed for CNV and chorioretinal burns lesion area by manually outlining the maximum border of each lesion and normalising against the optic nerve head. Net fluorescence above background and derived value of area corrected lesion intensity were calculated.

RESULTS: CNV lesions of rats treated with anti-VEGF antibody were significantly smaller in normalised lesion area ($p < 0.001$) and fluorescent intensity ($p < 0.001$) than the PBS treated control two weeks post laser. The calculated area corrected lesion intensity was significantly smaller ($p < 0.001$) in anti-VEGF treated animals at 2 and 3 weeks post laser. The results obtained using FFA correlated with, and were confirmed by conventional lesion area measurements from isolectin stained choroidal flatmounts, where lesions of anti-VEGF treated rats were significantly smaller at 2 weeks ($p = 0.049$) and 3 weeks ($p < 0.001$) post laser.

CONCLUSION: The presented method of in-vivo FFA quantification of CNV, including acquisition variable corrections, using the Micron III system and common use software establishes a reliable method for detecting and quantifying CNV enabling longitudinal studies and represents an important alternative to conventional CNV quantification methods.

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Pathogenesis

Toxicol In Vitro. 2015 May 26. [Epub ahead of print]

Methylglyoxal, a reactive glucose metabolite, enhances autophagy flux and suppresses proliferation of human retinal pigment epithelial ARPE-19 cells.

Chang YC, Hsieh MC, Wu HJ, Wu WC, Kao YH.

Abstract: Methylglyoxal (MGO), a glycolytic metabolite, induces oxidative injury and apoptotic cell death that play a pathogenetic role in age-related macular degeneration (AMD). This study examined the impact of MGO on cell proliferation and autophagy flux in retinal pigment epithelium (RPE) ARPE-19 cells and elucidated the underlying mechanism. Short-term MGO exposure suppressed cell proliferation without induction of apoptotic cell death, increased production of reactive oxygen species, and potentiated H₂O₂-exhibited cytotoxicity in ARPE-19 cells. Conversely, pretreatment with N-acetylcysteine, a ROS scavenger, and aminoguanidine, an MGO blocker, prevented MGO-induced growth retardation. MGO significantly enhanced autophagy flux and increased intracellular accumulation of autophagosomes, which was functionally confirmed by addition of autophagy enhancer or inhibitors. Signaling kinetic observation indicated that MGO remarkably triggered phosphorylation of Akt, ERK1/2, p38 MAPK, and JNK1/2. Blockade of kinase activity demonstrated that the hyperphosphorylation of Akt, ERK1/2, JNK, and p38 MAPK were all involved in the MGO-enhanced autophagy and growth-arresting effect in ARPE-19 cells. Moreover, pretreatment with autophagic flux inhibitors including 3-methyladenine, bafilomycin A, and chloroquine effectively ameliorated MGO- but not H₂O₂-mediated ARPE-19 cytotoxicity. In conclusion, modulation of autophagy flux activity by using autophagic or kinase inhibitors may be an applicable modality to treat AMD.

PMID: 26021238 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 May 1;56(5):3269-78.

Subducted and melanotic cells in advanced age-related macular degeneration are derived from retinal pigment epithelium.

Zanzottera EC, Messinger JD, Ach T, Smith RT, Curcio CA.

PURPOSE: To describe, illustrate, and account for two cell types plausibly derived from RPE in geographic atrophy (GA) and choroidal neovascularization (CNV) of AMD, using melanosomes, lipofuscin, and basal laminar deposit (BLamD) as anatomical markers.

METHODS: Human donor eyes with GA (n = 13) or CNV (n = 39) were histologically processed, photodocumented, and analyzed for frequencies of occurrence. We defined RPE as cells containing spindle-shaped melanosomes and RPE lipofuscin, internal to basal lamina or BLamD, if present, or Bruch's membrane if not, and RPE-derived cells as those plausibly derived from RPE and not attached to basal lamina or BLamD.

RESULTS: 'Subducted' cells contain RPE melanosomes and localize to the sub-RPE space, on Bruch's membrane. Credible transitional forms from RPE cells were seen. Grades of RPE overlying 'Subducted' cells were 'Atrophic with BLamD' (32.2% vs. 37.0% of 'Subducted,' for GA and CNV eyes, respectively), 'Dissociated' (22.0% vs. 21.7%), 'Nonuniform' (22.0% vs. 23.9%), and 'Sloughed' RPE (10.2% vs. 4.3%). Found exclusively in CNV scars, 'Melanotic' cells containing spherical melanosomes were adjacent to 'Entombed' RPE with spindle-shaped and spherical melanosomes. Of subretinal 'Melanotic' cells, 40.0% associated with 'Atrophy with BLamD,' 36.8% with 'Atrophy without BLamD,' and 20.6% with 'Entombed.'

CONCLUSIONS: 'Dissociated' RPE within atrophic areas may be the source of 'Subducted' cells. 'Entombed' RPE within fibrovascular and fibrocellular scars may be the source of 'Melanotic' cells. An imaging correlate for 'Subducted' cells awaits discovery; 'Melanotic' cells appear gray-black in the CNV fundus. Results provide a basis for future molecular phenotyping studies.

PMID: 26024109 [PubMed - in process]

Genetics

Genet Med. 2015 May 28. [Epub ahead of print]

Age-related macular degeneration: genome-wide association studies to translation.

Black JR, Clark SJ.

Abstract: In recent years, genome-wide association studies (GWAS), which are able to analyze the contribution to disease of genetic variations that are common within a population, have attracted considerable investment. Despite identifying genetic variants for many conditions, they have been criticized for yielding data with minimal clinical utility. However, in this regard, age-related macular degeneration (AMD), the most common form of blindness in the Western world, is a striking exception. Through GWAS, common genetic variants at a number of loci have been discovered. Two loci in particular, including genes of the complement cascade on chromosome 1 and the ARMS2/HTRA1 genes on chromosome 10, have been shown to convey significantly increased susceptibility to developing AMD. Today, although it is possible to screen individuals for a genetic predisposition to the disease, effective interventional strategies for those at risk of developing AMD are scarce. Ongoing research in this area is nonetheless promising. After providing brief overviews of AMD and common disease genetics, we outline the main recent advances in the understanding of AMD, particularly those made through GWAS. Finally, the true merit of these findings and their current and potential translational value is examined. *Genet Med* advance online publication 28 May 2015 *Genetics in Medicine* (2015); doi:10.1038/gim.2015.70.

PMID: 26020418 [PubMed - as supplied by publisher]

J Neurol Sci. 2015 May 9. [Epub ahead of print]

Evidence for a common founder effect amongst South African and Zambian individuals with Spinocerebellar ataxia type 7.

Smith DC, Atadzhanov M, Mwaba M, Greenberg LJ.

Abstract: Spinocerebellar ataxia type 7 (SCA7) is an inherited neurodegenerative disease caused by the expansion of a CAG repeat within the ataxin 7 gene, leading to a pathogenic polyglutamine tract within the ataxin 7 protein. SCA7 patients suffer from progressive cerebellar ataxia and macular degeneration. SCA7 is considered to be rare, although founder effects have been reported in South Africa, Scandinavia and Mexico. The South African SCA7-associated haplotype has not been investigated in any other populations, and there have been limited reports of SCA7 patients from other African countries. Here, we describe the first two ethnic Zambian families with confirmed SCA7. Haplotype analysis showed that the South African SCA7 haplotype alleles were significantly associated with the pathogenic expansion in affected Zambian individuals, providing strong evidence for a shared founder effect between South African and Zambian SCA7 patients.

PMID: 26003224 [PubMed - as supplied by publisher]

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