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MD Research News

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Drug treatment

Graefes Arch Clin Exp Ophthalmol. 2015 Mar 8. [Epub ahead of print] Change in vision after retinal pigment epithelium tear following the use of anti-VEGF therapy for age-related macular degeneration.

Durkin SR, Farmer LD, Kulasekara S, Gilhotra J.

PURPOSE: We investigated visual acuity outcomes and their associations in the setting of retinal pigment epithelium tear (RPET) following the use of anti-vascular endothelial growth factor (anti-VEGF) agents.

METHODS: This retrospective review included all patients treated for neovascular age-related macular degeneration (AMD) with an anti-VEGF agent who subsequently developed an RPET. All patients who developed an RPET were identified and outcome measures data were recorded and analysed. The main outcome measures were best corrected visual acuity (BCVA) and spectral domain optical coherence tomography characteristics.

RESULTS: Among the 14 participants identified, a subfoveal RPET was associated with the loss of one or more lines of vision from baseline ($p = 0.03$). There was no association between the size of the RPET and BCVA at the time of the RPET or final BCVA. The development of a disciform scar was associated both with a BCVA at the time of the RPET of < 6/24 ($p = 0.02$) and a final BCVA of < 6/24 ($p = 0.02$). Ongoing treatment with an anti-VEGF agent following an RPET saw five patients (35.7 %) have an improvement in their BCVA and all patients maintained their BCVA following the RPET with ongoing anti-VEGF treatment.

CONCLUSIONS: Visual decline following an RPET is associated with subfoveal location of the RPET ($p = 0.03$) and later development of a disciform scar. These data also suggest that the ongoing use of an anti-VEGF agent may stabilise vision in some patients following an RPET and for some patients there may be an improvement in visual acuity despite the RPET, depending on its location.

PMID: 25749721 [PubMed - as supplied by publisher]

Eur J Pharm Biopharm. 2015 Mar 7. [Epub ahead of print] Nanoparticles for the treatment of ocular neovascularizations.

Hennig R, Goepferich A

Abstract: Neovascular diseases of the posterior eye like age-related macular degeneration, proliferative diabetic retinopathy or retinopathy of prematurity carry a tremendous burden for patient and health care system alike. Although intravitreal injections of anti-VEGF based therapeutics have significantly improved

the visual outcome for many patients, current therapeutic options still show significant drawbacks such as the injection-related risk of contracting an infection. Due to their ability to encapsulate drugs with otherwise poor bioavailability, accumulate in areas of increased vascular permeability and control the release of active ingredients over time, nanoparticle systems have been widely researched to enhance current therapeutic strategies and expand the therapeutic arsenal. In this review, emphasis is placed both on the possibilities and drawbacks that a systemic nanoparticle-based therapy could have in the context of neovascular posterior eye diseases. Recent investigations into intravenous and intravitreal administration of nanomaterials and their potential to deliver potent drugs and genes to pathologic lesions will also be presented. Furthermore, we will focus on the exceptional anti-oxidative and anti-angiogenic properties of selected nanoscale systems that carve out new paths for the treatment of these severe posterior eye diseases.

PMID: 25758124 [PubMed - as supplied by publisher]

Expert Opin Drug Deliv. 2015 Mar 9:1-14. [Epub ahead of print] Cubosomes and other potential ocular drug delivery vehicles for macromolecular therapeutics.

Hartnett TE, O'Connor AJ, Ladewig K.

Abstract: Introduction: Many macromolecular therapeutics designed to treat posterior segment eye diseases (PSEDs) are administered through frequent ocular injection, which can further deteriorate eye health. Due to the high frequency of injection and the high cost of the therapeutics, there is a need to develop new ways in which to deliver these therapeutics: ways which are both safer and more cost effective. Areas covered: Using the most common PSED, age-related macular degeneration, as an example of a debilitating ocular disease, this review examines the key barriers limiting the delivery of macromolecular therapeutics to the posterior segment of the eye and defines the key requirements placed on particulate drug delivery vehicles (DDVs) to be suitable for this application. Recent developments in macromolecular drug delivery to treat this disease as well as the remaining shortcomings in its treatment are surveyed. Lastly, an emerging class of DDVs potentially suited to this application, called cubosomes, is introduced. Expert opinion: Based on their excellent colloidal stability and high internal surface area, cubosomes hold great potential for the sustained release of therapeutics. Novel production methods and a better understanding of the mechanisms through which drug release from these particles can be controlled are two major recent developments toward successful application.

PMID: 25745885 [PubMed - as supplied by publisher]

Acta Pol Pharm. 2014 Nov-Dec;71(6):900-16.

AMD--the retinal disease with an unprecised etiopathogenesis: in search of effective therapeutics.

Nowak JZ.

Abstract: AMD (age-related macular degeneration) is a progressive vision-threatening ocular disease, affecting central region of the retina--the macula--and manifesting in the elderly. AMD is a degenerative disease, and the degeneration affects primarily the retinal pigment epithelial (RPE) cells and secondarily the photoreceptors, leading consequently to disturbances or partial loss of central vision and legal blindness. Clinically, the disease is classified as: atrophic--dry AMD (in majority of cases), and neovascular--wet AMD (with choroidal neovascularization--CNV: 10-15% of all AMD cases). Pathogenesis of AMD is complex, multifactorial and only poorly recognized. Main risk factors include: advanced age, genetic predispositions, environmental determinants, history of exposure to intensive light and smoking. At least four molecular processes contribute to the development of AMD pathology: lipofuscinogenesis, drusogenesis, inflammation and choroidal neovascularization (in wet AMD). Since vascular endothelial growth factor (VEGF) is a predominant proangiogenic factor in CNV. the wet AMD can be treated with intravitreous application of "anti-VEGF" agents (Avastin, Lucentis, Eylea). Till now, there is no approved

therapy for dry AMD, although several agents/treatments are currently in clinical trials. This paper briefly describes major molecular and cellular events leading to AMD, and presents currently used and new experimental therapeutic strategies against AMD.

PMID: 25745762 [PubMed - in process]

Eye (Lond). 2015 Mar;29(3):450-1. doi: 10.1038/eye.2014.321.

Two-year outcome of an observe-and-plan regimen for neovascular age-related macular degeneration: how to alleviate the clinical burden with maintained functional results.

Gianniou C, Dirani A, Ferrini W, Marchionno L, Decugis D, Deli A, Ambresin A, Mantel I.

PMID: 25762129 [PubMed - in process]

Other treatment & diagnosis

Clin Exp Optom. 2015 Mar 10. [Epub ahead of print] What percentage of patients presenting for routine eye examinations require referral for secondary care? A study of referrals from optometrists to ophthalmologists.

Dobbelsteyn D, McKee K, Bearnes RD, Jayanetti SN, Persaud DD, Cruess AF.

BACKGROUND: The aim was to investigate the percentage of asymptomatic patients presenting for routine optometric eye examinations that have pathology or pathology-related risk factors warranting referral for ophthalmological consultation.

METHODS: This was a retrospective, cohort case study and the inclusion criteria for participants included: (i) the patient presented for routine optometric eye care during a specified period of time; (ii) the patient was found to have pathology (or showed enough risk of pathology) resulting in referral to an ophthalmologist; and (iii) a referral report was received from the consulting ophthalmologist stating the diagnosis and the treatment plan. The data set was further reviewed to indicate presenting symptoms and patient age. Adult patients, ages 20 to 64 years, were reviewed separately; this age group is not covered by provincial health services for routine eye care in Nova Scotia. Files were obtained from two clinics through an electronic charting program. A database was created that included date of referral, clinical reasons for the referral, diagnosis and treatment plan. Clinical reasons for referral were extracted from the referral letters and reports and sorted into six disease categories: age-related macular degeneration, cataract, glaucoma, diabetic retinopathy, retinopathy and 'other'.

RESULTS: The overall referral rate for the combined data set was nine per cent for all ages; 2.4 per cent of the overall patients were asymptomatic. There was a similar number of asymptomatic patients referred in the adult (20 to 64 years) age group compared to all ages (2.5 per cent).

CONCLUSION: A significant number of patients that present for routine eye examinations without any symptoms indicative of ocular disease are subsequently found to have a degree of pathology or risk thereof requiring referral for ophthalmological consultation. These referrals occur for adults under 64 years as much as for all patients of all ages.

PMID: 25756613 [PubMed - as supplied by publisher]

J Refract Surg. 2015 Mar;31(3):158-62.

Initial Clinical Results of a New Telescopic IOL Implanted in Patients With Dry Age-Related Macular Degeneration.

Hengerer FH, Artal P, Kohnen T, Conrad-Hengerer I.

PURPOSE: To evaluate the safety and efficacy of the iol-AMD technology (London Eye Hospital Pharma, London, UK), which includes two injectable, hydrophobic acrylic intraocular lenses (IOLs) in a pilot study of patients diagnosed as having cataract and dry age-related macular degeneration.

METHODS: The cataract surgery and IOL implantation were performed after a preoperative evaluation using the iolAMD simulator in eyes with bilateral intermediate dry age-related macular degeneration. Outcomes were intraoperative and postoperative complications, subjective and objective visual acuity improvement, visual field changes, and postoperative diplopia.

RESULTS: Three eyes of 2 patients were evaluated. The surgeries were uneventful. All eyes gained monocular reading vision at the 1-week postoperative visit. One patient with monocular implantation recognized diplopia for distance vision. Preoperative corrected distance visual acuity ranged from 20/800 to 20/125 and corrected near visual acuity was 20/800 or less. Two months after surgery, corrected distance and near visual acuities increased to levels between 20/40 and 20/25 (uncorrected distance visual acuity was 20/60 to 20/32; uncorrected near visual acuity was 20/200 to 20/25).

CONCLUSIONS: These early results showed that the iolAMD simulator is a promising technology improving near and distance visual acuity in eyes with intermediate dry macular degeneration. The prismatic IOL effect did not lead to diplopia when implanted bilaterally. The surgery was safely performed.

PMID: 25751831 [PubMed - in process]

Related citations

Pathogenesis

JAMA Ophthalmol. 2015 Mar [Epub ahead of print] Reticular Pseudodrusen Associated With a Diseased Bruch Membrane in Pseudoxanthoma Elasticum.

Gliem M, Hendig D, Finger RP, Holz FG, Issa PC

IMPORTANCE: Reticular pseudodrusen (RPD) are frequently associated with age-related macular degeneration and considered to be an independent risk factor for disease progression, but the pathophysiologic mechanisms are only incompletely understood. Therefore, it may be helpful to identify the associations of RPD with other diseases that have defined pathophysiologic mechanisms.

OBJECTIVE: To describe the phenotype, prevalence, and topographic distribution of RPD in patients with pseudoxanthoma elasticum (PXE) and their association with a diseased Bruch membrane.

DESIGN, SETTING, AND PARTICIPANTS: In this single-center, prospective, cross-sectional case series, 57 consecutive patients with PXE from a university referral center whose diagnosis has been confirmed by genetic testing and/or skin biopsy were studied from March 1, 2013, through February 28, 2014.

MAIN OUTCOMES AND MEASURES: Phenotypic characteristics of RPD were evaluated with multiple imaging techniques. The RPD were defined as irregular networks of round to oval lesions that appear hyporeflective on near-infrared reflectance, hypoautofluorescent on fundus autofluorescence, and as subretinal deposits on spectral-domain optical coherence tomographic images. The presence of RPD was judged based on characteristic findings in at least 2 of the 3 imaging modalities.

RESULTS: A total of 57 patients were examined, and 15 patients were excluded mainly because of large central atrophy or fibrosis. In the remaining 42 patients with PXE, RPD were detected in 22 patients (52%; 95% CI, 38%-67%). Prevalence of RPD was highest in the fifth decade at 67% (10/15; 95% CI, 42%-85%). The RPD were most frequently located within the superior quadrant and least frequently located within the central macula. The RPD were always located central to areas with peau d'orange and within an area of hypofluorescence on late-phase indocyanine green angiographic images.

CONCLUSIONS AND RELEVANCE: These data suggest that RPD have a high prevalence in eyes of patients with PXE. Although RPD in patients with PXE occur at a younger age, their distribution and phenotype appear to be similar to RPD associated with age-related macular degeneration. The association with diseased Bruch membrane in PXE suggests a pathogenetic role of Bruch membrane alterations for the development of RPD.

PMID: 25764262 [PubMed]

Curr Neurovasc Res. 2015 Mar 10. [Epub ahead of print] An experimental model for exudative age-related macular degeneration with choroidal neovascularization using the common marmoset.

Shimazawa M, Masuda T, Nakamura S, Miwa M, Nakamura K, Hara H.

Abstract: This study aimed to establish an experimental exudative age-related macular degeneration (AMD) model in the common marmoset (Callithrix jacchus), which is a small New World monkey. Choroidal neovascularization (CNV) was induced by laser irradiation on the left eye of each animal under anesthesia. Eight laser spots were applied around the macular area using the image-guided laser system (532 nm) attached with Micron III at 650 mW-2,000 mW power. Laser pulse duration and spot size were fixed at 100 ms and 50 μm, respectively. At 14 days after laser irradiation, fluorescein angiograms were observed. At 21 days after laser irradiation, the fluorescein angiograms were transcardially perfused to the bilateral common carotid arteries with 4% paraformaldehyde for the transverse section or with fluorescein-conjugated dextran (MW = 2,000 kDa) for the retinal pigment epithelia (RPE)-choroidal flatmount. At 14 days after laser irradiation, late hyperfluorescence and leakage within or beyond the lesion borders were observed in a laser power-dependent manner. In the RPE-choroidal flatmount, the mean size of the CNV lesions at 1,500 mW was 1.34 ± 0.49 × 105 μm2 (Mean ± S.D., n = 29), and the coefficient of variation for each CNV area was 36.5% (n = 29). In conclusion, we succeeded in producing an experimental exudative type of AMD model in the common marmoset. This model may be useful in elucidating the pathophysiological mechanism and screening of new candidates for exudative AMD.

PMID: 25760220 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Mar 10. [Epub ahead of print] Inner segment remodeling and mitochondrial translocation in cone photoreceptors in age-related macular degeneration with outer retinal tubulation.

Litts KM, Messinger JD, Freund KB, Zhang Y, Curcio CA

PURPOSE: By examining cone inner segment (IS) ultrastructure, to quantify impressions of mitochondrial translocation in degenerating cones, and to determine the nature of accumulated material in the subretinal space with apparent IS-like features.

METHODS: Human donor eyes with advanced age-related macular degeneration (AMD) were screened for outer retinal tubulation (ORT) in macula-wide high-resolution digital sections. Degenerating cones inside (ORT cones) and outside ORT (NonORT cones) from AMD eyes, and unaffected cones in age-matched Control eyes were imaged using transmission electron microscopy. The distances of mitochondria to the external limiting membrane (ELM), cone IS length, and cone IS width at the ELM were measured.

RESULTS: ORT and NonORT cones lose outer segments (OS), followed by shortening of IS and mitochondria. In NonORT cones, IS broaden. ORT and NonORT cone IS myoids become undetectable due to mitochondria re-distribution toward the nucleus. Some ORT cones lacked IS and contained mitochondria in the outer fiber (between soma and ELM). Unlike long thin IS mitochondria in Control cones, ORT and NonORT IS mitochondria are ovoid and reniform. Shed IS, some containing mitochondria, were found in the subretinal space.

CONCLUSION: In AMD, macula cones exhibit loss of detectable myoid due to IS shortening in addition to

OS loss, as described. Mitochondria shrink and translocate toward the nucleus. As reflectivity sources, translocating mitochondria may be detectable using in vivo imaging to monitor photoreceptor degeneration in retinal disorders. These results improve the knowledge basis for interpreting high-resolution clinical retinal imaging.

PMID: 25758815 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Mar 10. [Epub ahead of print] Lipofuscin re-distribution and loss accompanied by cytoskeletal stress in retinal pigment epithelium of eyes with age-related macular degeneration.

Ach T, Tolstik E, Messinger JD, Zarubina AV, Heintzmann R, Curcio CA.

PURPOSE: Lipofuscin (LF) and melanolipofuscin (MLF) of the retinal pigment epithelium (RPE) are the principal sources of autofluorescence (AF) signals in clinical fundus-AF imaging. Few details about the subcellular distribution of AF organelles in age-related macular degeneration (AMD) are available. We describe the impact of aging and AMD on RPE morphology revealed by the distribution of AF LF/MLF granules and actin cytoskeleton in human tissues.

METHODS: Thirty-five RPE-Bruch's membrane flatmounts from 35 donors were prepared (post-mortem: ≤ 4 hours). Ex vivo fundus examination at the time of accession revealed either absence of chorioretinal pathologies (10 tissues; mean age: 83.0 ± 2.6 years) or stages of AMD (25 tissues; 85.0±5.8 years): early AMD, geographic atrophy, and late exudative AMD. RPE cytoskeleton was labeled with AlexaFluor647-Phalloidin. Tissues were imaged on a spinning-disk fluorescence microscope and a high resolution structured illumination microscope.

RESULTS: AMD impacts individual RPE cells by: 1) lipofuscin re-distribution by a) degranulation (granule-by-granule loss) and/or b) aggregation and apparent shedding into the extracellular space; 2) enlarged RPE cell area and conversion from convex to irregular and sometimes concave polygons; 3) cytoskeleton derangement including separations and breaks around subretinal deposits, thickening, and stress fibers.

CONCLUSIONS: We report an extensive and systematic en face analysis of LF/MLF-AF in AMD eyes. Re-distribution and loss of AF granules are among the earliest AMD changes and could reduce fundus AF signal attributable to RPE at these locations. Data can enhance the interpretation of clinical fundus-AF and provide a basis for future quantitative studies.

PMID: 25758814 [PubMed - as supplied by publisher]

Ocul Immunol Inflamm. 2015 Mar 11:1. [Epub ahead of print] Response to the Letter of Dr. Mehmet Agilli et al.: Elevated Plasma Pentraxin3 Levels and Its Association with Neovascular Age-related Macular Degeneration.

Min JK, Kim J, Woo JM

PMID: 25760912 [PubMed - as supplied

Epidemiology

PLoS One. 2015 Mar 6;10(3):e0120003.

Association between Neovascular Age-Related Macular Degeneration and Dementia: A Population-Based Case-Control Study in Taiwan.

Chung SD, Lee CZ, Kao LT, Lin HC, Tsai MC, Sheu JJ.

BACKGROUND: Most available studies focusing on the association between neovascular age-related macular degeneration (AMD) and dementia have conflicting results. This study aimed to investigate the association between previously diagnosed AMD and dementia using a population-based dataset in Taiwan.

METHODS: Data for this case-control study were retrospectively collected from the Taiwan National Health Insurance Research Database. We identified 13,402 subjects who had a diagnosis of dementia as cases, and 40,206 subjects without dementia as controls. A conditional logistic regression was used to examine the association of dementia with previously diagnosed neovascular AMD.

RESULTS: We found that of the study sample of 53,608 subjects, 1.01% had previously diagnosed neovascular AMD, 1.35% and 0.90% for cases and the controls, respectively ($p<0.001$). The conditional logistic regression analysis suggested that the odds ratio of prior neovascular AMD for cases was 1.37 (95% confidence interval: 1.14~1.65) compared to the controls after adjusting for subjects' age, monthly income, geographic location, urbanization level, and hyperlipidemia, diabetes, hypertension, stroke, ischemic heart disease, and whether or not a subjects underwent cataract surgery prior to index date than controls.

CONCLUSIONS: Dementia subjects were associated with a higher proportion of prior neovascular AMD than were the controls.

PMID: 25748702 [PubMed - in process]

Genetics

Int J Legal Med. 2015 Mar 13. [Epub ahead of print] Potential relationship between single nucleotide polymorphisms used in forensic genetics and diseases or other traits in European population.

Pombar-Gomez M, Lopez-Lopez E, Martin-Guerrero I, Carles AG, de Pancorbo MM.

Abstract: Single nucleotide polymorphisms (SNPs) are an interesting option to facilitate the analysis of highly degraded DNA by allowing the reduction of the size of the DNA amplicons. The SNPforID 52-plex panel is a clear example of the use of non-coding SNPs in forensic genetics. However, nonstop advances in studies of genetic polymorphisms are leading to the discovery of new associations between SNPs and diseases. The aim of this study was to perform a comprehensive review of the state of association between the 52 SNPs in the 52-plex panel and diseases or other traits related to their treatment, such as drug response characters. In order to achieve this goal, we have conducted a bioinformatic search for each SNP included in the panel and the SNPs in linkage disequilibrium (LD) with them in the European population ($r^2 > 0.8$). A total of 424 SNPs (52 in the panel and 372 in LD) were investigated in PubMed, Scopus, and dbSNP databases. Our results show that three SNPs in the SNPforID 52-plex panel (rs2107612, rs1979255, rs1463729) have been associated with diseases such as hypertension or macular degeneration, as well as drug response. Similarly, three out of the 372 SNPs in LD (rs2107614, $r^2 = 0.859$; rs765250, $r^2 = 0.858$; rs11064560, $r^2 = 0,887$) are also associated with various pathologies. In view of these results, we propose the need for a periodic review of the SNPs used in forensic genetics in order to keep their associations with diseases or related phenotypes updated and to evaluate their continuity in forensic panels for avoiding legal and ethical conflicts.

PMID: 25763762 [PubMed - as supplied by publisher]

Diet, lifestyle and low vision

J Agric Food Chem. 2015 Mar 13. [Epub ahead of print] Bioaccessibility and Digestive Stability of Carotenoids in Cooked Eggs Studied Using a Dynamic in Vitro Gastrointestinal Model.

Nimalaratne C, Savard P, Gauthier SF, Schieber A, Wu J.

Abstract: Among dietary carotenoids, lutein and zeaxanthin are known to protect against age-related macular degeneration, a leading cause of irreversible vision loss in the elderly. Egg yolk is rich in lutein and zeaxanthin, however, the effect of cooking and gastrointestinal digestion on yolk carotenoids is poorly understood. An in vitro dynamic gastrointestinal model (TIM-1) was used to investigate the digestive stability and bioaccessibility of carotenoids from boiled, fried, and scrambled eggs. Bioaccessibility but not digestive stability was significantly affected by the method of cooking. The main egg carotenoids, all-E-lutein and all-E-zeaxanthin, were stable during the digestion with average recoveries of 90 and 88%, respectively. No trans-cis isomerization of carotenoids was observed during digestion. Both all-E-lutein and all-E-zeaxanthin from scrambled eggs showed significantly lower bioaccessibility compared to boiled eggs. The results indicate that the bioaccessibility of egg carotenoids can be affected by different food preparation methods.

PMID: 25748723 [PubMed - as supplied by publisher]