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MD Research News

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Drug treatment

Retina. 2016 Apr 28. [Epub ahead of print]

PROGRESSION OF MACULAR ATROPHY IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION UNDERGOING ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY.

Abdelfattah NS, Zhang H, Boyer DS, Sadda SR.

PURPOSE: To define the frequency and quantify the progression of macular atrophy (MA) in patients with neovascular age-related macular degeneration undergoing treatment with antivascular endothelial growth factor therapy for >2 years.

METHODS: Fifty-four eyes of 46 patients (86.7 ± 6.8 years, 53.7% women) diagnosed with wet age-related macular degeneration were included in this retrospective study. Eyes that received photodynamic therapy or laser treatment were excluded. All eyes were imaged at baseline and after 2 years with the Cirrus spectral domain optical coherence tomography using a 512 × 128 macular cube scan protocol centered on the fovea. Optical coherence tomography en face fundus images were obtained for each 3-dimensional data set using the U.S. Food and Drug Administration-cleared Advanced RPE Analysis software, which automatically identifies atrophic areas by segmenting regions of increased reflectivity in en face choroidal slab images. Segmentation errors were manually corrected by trained Doheny Image Reading Center graders using a standardized grading protocol. The prevalence rates of atrophy at baseline and at 2-years follow-up and enlargement rates were computed. Baseline demographic factors and types and numbers of antivascular endothelial growth factor injections received over time were correlated with the development and enlargement of atrophy.

RESULTS: Macular atrophy was noted at baseline in 32 (59.3%) eyes and progressed in all eyes over the next 2 years. Among the 28 eyes without atrophy at baseline, MA developed by 2 years in 6 eyes (21.4% of eyes without MA at baseline). Of note, 22 eyes (40.7% of overall cohort) never developed atrophy during the course of the study. Among eyes with atrophy at baseline, the annual growth rate of MA was found to be 0.89 ± 0.93 mm. A multiple regression analysis was performed to evaluate the influence of gender, age, smoking status, medication injected, and number of injections on MA. Except for the number of total injections ($R = 0.3$, $P < 0.01$), the studied variables could not significantly predict development or progression of MA ($F [0.73, 13] = 0.378$, $P = 0.86$, $R = 0.05$). However, the study was not powered to detect small effects.

CONCLUSION: Macular atrophy is a frequent finding in eyes with wet age-related macular degeneration both before and after antivascular endothelial growth factor therapy. The frequency of new optical coherence tomography-defined atrophy (21% at 2 years) after starting therapy was close to the rates reported in CATT, IVAN, and HARBOR. The rate of MA enlargement was positively correlated with the number of injections, but did not appear to be greater than that reported for atrophy in the absence of choroidal neovascularization.

PMID: 27135213 [PubMed - as supplied by publisher]

Retina. 2016 Apr 29. [Epub ahead of print]

ANTERIOR CHAMBER FLARE DURING BEVACIZUMAB TREATMENT IN EYES WITH EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

Hautamäki A, Luoma A, Immonen I.

PURPOSE: To study the anterior chamber flare during bevacizumab treatment of exudative age-related macular degeneration.

METHODS: During a 2-year prospective follow-up, 50 patients recently diagnosed with exudative age-related macular degeneration were treated at once-a-month visits if subretinal or intraretinal fluid or a new hemorrhage was present in the lesion area. Flare was measured weekly during the first month and then monthly in both eyes.

RESULTS: Higher flare was associated with older age (P = 0.007, Linear Mixed Model), higher number of smoking pack-years (P = 0.019), macular cysts (P = 0.041), and pseudophakia (P = 0.003). The levels gradually increased during the follow-up (P < 0.0001) but less in the eyes with classic CNV (P = 0.011). Flare decreased during treatment-free periods lasting for at least two consecutive visits (P = 0.005). A peak in flare was observed 1 week after the first injection (P = 0.034, Wilcoxon signed rank test). In the fellow eyes, higher flare values in the beginning of the follow-up were associated with later conversion into exudative age-related macular degeneration (P = 0.015, Mann-Whitney U test).

CONCLUSION: Anterior chamber flare correlated poorly with the CNV activity. Higher levels may, however, precede or exist early in the process that leads to the development of exudative age-related macular degeneration.

PMID: 27135211 [PubMed - as supplied by publisher]

Sci Rep. 2016 May 5;6:25509.

A novel small molecule ameliorates ocular neovascularisation and synergises with anti-VEGF therapy.

Sulaiman RS, Merrigan S, Quigley J, Qi X, Lee B, Boulton ME, Kennedy B, Seo SY, Corson TW.

Abstract: Ocular neovascularisation underlies blinding eye diseases such as retinopathy of prematurity, proliferative diabetic retinopathy, and wet age-related macular degeneration. These diseases cause irreversible vision loss, and provide a significant health and economic burden. Biologics targeting vascular endothelial growth factor (VEGF) are the major approach for treatment. However, up to 30% of patients are non-responsive to these drugs and they are associated with ocular and systemic side effects. Therefore, there is a need for small molecule ocular angiogenesis inhibitors to complement existing therapies. We examined the safety and therapeutic potential of SH-11037, a synthetic derivative of the antiangiogenic homoisoflavonoid cremastranone, in models of ocular neovascularisation. SH-11037 dose-dependently suppressed angiogenesis in the choroidal sprouting assay ex vivo and inhibited ocular developmental angiogenesis in zebrafish larvae. Additionally, intravitreal SH-11037 (1 μM) significantly reduced choroidal neovascularisation (CNV) lesion volume in the laser-induced CNV mouse model, comparable to an anti-VEGF antibody. Moreover, SH-11037 synergised with anti-VEGF treatments in vitro and in vivo. Up to 100 μM SH-11037 was not associated with signs of ocular toxicity and did not interfere with retinal function or pre-existing retinal vasculature. SH-11037 is thus a safe and effective treatment for murine ocular neovascularisation, worthy of further mechanistic and pharmacokinetic evaluation.

PMID: 27148944 [PubMed - in process]

Angiogenesis. 2016 May 4. [Epub ahead of print]

HIF inhibitors for ischemic retinopathies and cancers: options beyond anti-VEGF therapies.

Subhani S, Vavilala DT, Mukherji M.

Abstract: Aberrant activation of the hypoxia inducible factor (HIF) pathway causing overexpression of angiogenic genes, like vascular endothelial growth factor (VEGF), is one of the underlying causes of ocular neovascularization (NV) and metastatic cancer. Consistently, along with surgical interventions, a number of anti-VEGF agents have been approved by FDA for the treatment of ocular neovascular diseases. These anti-VEGF agents, like ranibizumab/lucentis, have revolutionized the treatment in the past decade. However, substantial vision improvement is observed only in a subset of age-related macular degeneration patients receiving ranibizumab. Further, all current therapies are associated with limitations and side effects. For example, surgeries cause tissue destruction and inflammation while anti-VEGF therapies are expensive, require repeated administration, and offer temporary relief from vascular leakage. These factors impose significant cost and treatment burdens to both the patient and society. With an aging population in most western countries with a continually increasing number of patients on lifelong treatment for these retinal diseases, the focus of ocular drug development for neovascular diseases will be to improve efficacy while reducing treatment costs. Blocking the HIF pathway, a major regulator of ocular NV and cancer, offers an appealing therapeutic strategy. Therefore, this review summarizes HIF inhibitors that have been recently evaluated for the treatment of different cancers and ischemic retinopathies.

PMID: 27146677 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2016 May 4. [Epub ahead of print]

Correction: Current therapeutic developments in atrophic age-related macular degeneration. [No authors listed]

Erratum for

Current therapeutic developments in atrophic age-related macular degeneration. [Br J Ophthalmol. 2016]

PMID: 27146155 [PubMed - as supplied by publisher]

Int Ophthalmol. 2016 May 6. [Epub ahead of print]

Subfoveal choroidal thickness changes after intravitreal bevacizumab injection for neovascular age -related macular degeneration and diabetic macular edema.

Ünlü C, Erdogan G, Gunay BO, Kardes E, Akcay BI, Ergin A.

Abstract: The purpose of this study was to investigate the changes in subfoveal choroidal thickness (SFCT) after intravitreal injection of bevacizumab (IVB) for neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME). This retrospective, consecutive, interventional case series study included 43 eyes [21 affected eyes with neovascular AMD (AMD group) and 22 affected eyes with DME (DME group)] which were treated with 1.25 mg/0.5 ml IVB and 43 untreated fellow eyes of 43 patients. SFCT was measured in all 86 eyes at baseline before IVB injection and at day 1, week 1, and month 1 after injection by use of enhanced depth imaging optical coherence tomography (EDI OCT). Central foveal thickness (CFT) and best-corrected visual acuity were analyzed at baseline and during follow-up visits. Main outcome measure was change in SFCT in 1 month after treatment. All 43 eyes treated with IVB showed a significant reduction in SFCT. Mean SFCT in treated eyes decreased from 237.1 ± 75.3 μm at baseline to 214.0 ± 65.7 μm at day 1, 205.4 ± 59.7 at week 1, and 222.7 ± 73.3 at month 1, whereas SFCT in fellow eyes changed from 228.4 ± 63.6 at baseline to 224.5 ± 68.5 at day 1, 220.4 ± 72.1 at week 1, and

226.9 ± 74.0 at month 1. SFCT demonstrated a similar trend toward decrease in both groups. CFT decreased significantly and visual acuity improved significantly. SFCT decreased significantly in AMD and DME eyes following injection. The decreasing effect of bevacizumab on choroidal thickness was highest at first week and continued to the end of first month after injection.

PMID: 27154721 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2016 Apr 18;10:695-6. eCollection 2016.

Comment on: "Three-year follow-up of ranibizumab treatment of wet age-related macular degeneration: influence of baseline visual acuity and injection frequency on visual outcomes".

Kaya A.

PMID: 27143846 [PubMed] PMCID: PMC4841436

Other treatment & diagnosis

Am J Ophthalmol. 2016 Apr 27. [Epub ahead of print]

Defining a Minimum Set of Standardized Patient-centered Outcome Measures for Macular Degeneration.

Rodrigues IA, Sprinkhuizen SM, Barthelmes D, Blumenkranz M, Cheung G, Haller J, Johnston R, Kim R, Klaver C, McKibbin M, Ngah NF, Pershing S, Shankar D, Tamura H, Tufail A, Weng CY, Westborg I, Yelf C, Yoshimura N, Gillies MC.

PURPOSE: To define a minimum set of outcome measures for tracking, comparing, and improving macular degeneration care.

DESIGN: Recommendations from working-group of international experts in macular degeneration outcomes registry development and patient advocates, facilitated by the International Consortium for Health Outcomes Measurement (ICHOM).

METHODS: Modified Delphi technique, supported by structured teleconferences, followed by online-surveys to drive consensus decisions. Potential outcomes were identified through literature review of outcomes collected in existing registries and reported in major clinical trials. Outcomes were refined by the working-group and selected based upon impact on patients, relationship to good clinical care and feasibility of measurement in routine clinical practice.

RESULTS: Standardized measurement of the following outcomes is recommended: visual functioning and quality of life (distance visual acuity, mobility and independence, emotional well-being, reading and accessing information); number of treatments; complications of treatment; and disease-control. Proposed data-collection sources include administrative, clinical data during routine clinical visits and patient-reported sources annually. Recording the following clinical characteristics is recommended to enable risk-adjustment: age; gender; ethnicity; smoking status; baseline visual acuity in both eyes; type of macular degeneration; presence of geographic atrophy, subretinal fibrosis or pigment epithelial detachment; previous macular degeneration treatment; ocular co-morbidities.

CONCLUSIONS: The recommended minimum outcomes and pragmatic reporting standards should enable standardized, meaningful assessments and comparisons of macular degeneration treatment outcomes. Adoption could accelerate global improvements in standardized data-gathering and reporting of patient-centered outcomes. This can facilitate informed decisions by patients and health care providers, plus allow long-term monitoring of aggregate data, ultimately improving understanding of disease progression and

treatment responses.

PMID: 27131774 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2016 May 3. [Epub ahead of print]

EVEREST study report 3: diagnostic challenges of polypoidal choroidal vasculopathy. Lessons learnt from screening failures in the EVEREST study.

Tan CS, Ngo WK, Lim LW, Tan NW, Lim TH; EVEREST Study Group.

PURPOSE: To describe screening failures in the EVEREST study by examining the imaging characteristics that enabled differentiation of polypoidal choroidal vasculopathy (PCV) from cases that were subsequently diagnosed not to be PCV.

METHODS: Post-hoc analysis of 34 patients with PCV reported as screening failures from EVEREST study. Standardised confocal scanning laser indocyanine green angiography (ICGA) images were graded by the Central Reading Centre to confirm PCV diagnosis based on the presence of early focal sub-retinal hyperfluorescence on ICGA and at least one of the following six diagnostic criteria: (1) nodular appearance of polyp(s) on stereoscopic examination, (2) hypofluorescent halo around nodule(s), (3) presence of a branching vascular network, (4) pulsation of polyp(s) on dynamic ICGA, (5) orange sub-retinal nodules on colour fundus photography, or (6) massive sub-macular haemorrhage (≥4 disc areas in size). Additional detailed image grading was performed with stereo-imaging and dynamic early-phase ICGA.

RESULTS: Of the 95 screened PCV cases, 34 were excluded: (1) cases not suitable for recruitment as per the study protocol (n = 14), (2) equivocal lesions on ICGA characterised by small hyperfluorescent dots (n = 9), and (3) cases that were definitely not PCV (non-PCV, n = 11), identified by definitive diagnoses which included one case each of micro-aneurysm, retinal angiomatous proliferation, retino-choroidal anastomosis, small type-2 choroidal neovascularisation, retinal pigment epithelial (RPE) window defect and disciform scar; two cases of lesions where the choroidal vessel changed its course; and three cases of late-onset RPE staining.

CONCLUSIONS: Standardised image grading techniques used in EVEREST study enabled effective differentiation of non-PCV from actual PCV.

PMID: 27142805 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2016 May 1;57(6):2479-87.

Autofluorescence Lifetimes in Geographic Atrophy in Patients With Age-Related Macular Degeneration.

Dysli C, Wolf S, Zinkernagel MS.

PURPOSE: To investigate fluorescence lifetime characteristics in patients with geographic atrophy (GA) in eyes with age-related macular degeneration and to correlate the measurements with clinical data and optical coherence tomography (OCT) findings.

METHODS: Patients with GA were imaged with a fluorescence lifetime imaging ophthalmoscope. Retinal autofluorescence lifetimes were measured in a short and a long spectral channel (498-560 nm and 560-720 nm). Mean retinal fluorescence lifetimes were analyzed within GA and the surrounding retina, and data were correlated with best corrected visual acuity and OCT measurements.

RESULTS: Fluorescence lifetime maps of 41 eyes of 41 patients (80 ± 7 years) with GA were analyzed. Mean lifetimes within areas of atrophy were prolonged by 624 ± 276 ps (+152%) in the short spectral

channel and 418 ± 186 ps (+83%) in the long spectral channel compared to the surrounding tissue. Autofluorescence lifetime abnormalities in GA occurred with particular patterns, similar to those seen in fundus autofluorescence intensity images. Within the fovea short mean autofluorescence lifetimes were observed, presumably representing macular pigment. Short lifetimes were preserved even in the absence of foveal sparing but were decreased in patients with advanced retinal atrophy in OCT. Short lifetimes in the fovea correlated with better best corrected visual acuity in both spectral channels.

CONCLUSIONS: This study established that autofluorescence lifetime changes in GA present with explicit patterns. We hypothesize that the short lifetimes seen within the atrophy may be used to estimate damage induced by atrophy and to monitor disease progression in the context of natural history or interventional therapeutic studies.

PMID: 27149697 [PubMed - in process]

Pathogenesis

Biochim Biophys Acta. 2016 May 4. [Epub ahead of print]

Review: adiponectin in retinopathy.

Fu Z, Gong Y, Löfqvist C, Hellström A, Smith LE.

Abstract: Neovascular eye diseases are a major cause of blindness including retinopathy of prematurity, diabetic retinopathy and age-related macular degeneration in which new vessel formation is driven by hypoxia or metabolic abnormalities affecting the fuel supply. White-adipose-tissue derived adipokines such as adiponectin modulate metabolic responses. Increasing evidence shows that lack of adiponectin may result in retinal neovascularization. Activation of the adiponectin pathway may in turn restore energy metabolism, to suppress the drive for compensatory but ultimately pathological neovessels of retinopathy. In this review, we will summarize our current knowledge of the role of adiponectin in eye diseases of premature infants, diabetic patients as well as the elderly. Further investigations in this field are likely to lead to new preventative approaches for these diseases.

PMID: 27155572 [PubMed - as supplied by publisher]

Life Sci. 2016 May 4. [Epub ahead of print]

Lycopene inhibits ICAM-1 expression and NF-κB activation by Nrf2-regulated cell redox state in human retinal pigment epithelial cells.

Yang PM, Wu ZZ, Zhang YQ, Wung BS.

AIMS: Age-related macular degeneration (AMD) is one of the most common diseases leading to blindness in elderly people. The progression of AMD may be prevented through anti-inflammation and antioxidation in retinal pigment epithelial (RPE) cells. Lycopene, a carotenoid, has been shown to possess both antioxidative and anti-inflammatory properties. This research was conducted to detail the mechanisms of these effects of lycopene-treated RPE cells.

MAIN METHODS: We exposed ARPE-19 cells to TNFα after pretreatment with lycopene, and measured monocyte adhesion, ICAM-1 expression, NF-κB nuclear translocation, and transcriptional activity. Cell viability was assayed with Alamar Blue. The cell redox state was tested by glutathione (GSH) and reactive oxygen species (ROS) levels. The importance of the Nrf2 pathway was tested in nuclear translocation, promoter reporter assay, and siRNA.

KEY FINDINGS: Lycopene could reduce TNF-α-induced monocyte adhesion and H2O2- induced cell

damage in RPE cells. Furthermore, lycopene inhibits ICAM-1 expression and abolishes NF-κB activation for up to 12h in TNFα-treated RPE cells. Lycopene upregulates Nrf2 levels in nuclear extracts and increases the transactivity of antioxidant response elements. The use of Nrf2 siRNA blocks the inhibitory effect of lycopene in TNF-α-induced ICAM-1 expression and NF-κB activation. Glutamate-cysteine ligase (GCL) is the rate-limiting enzyme in the de novo synthesis of GSH. We found that lycopene increases intracellular GSH levels and GCL expression. Following lycopene treatment, TNF-α-induced ROS production was abolished.

SIGNIFICANCE: The Nrf2-regulated antioxidant property plays a pivotal role in the anti-inflammatory mechanism underlying the inhibition of NF-κB activation in lycopene-treated ARPE-19 cells.

PMID: 27155396 [PubMed - as supplied by publisher]

EMBO Mol Med. 2016 May 3. [Epub ahead of print]

Interferon-beta signaling in retinal mononuclear phagocytes attenuates pathological neovascularization.

Lückoff A, Caramoy A, Scholz R, Prinz M, Kalinke U, Langmann T.

Abstract: Age-related macular degeneration (AMD) is a leading cause of vision loss among the elderly. AMD pathogenesis involves chronic activation of the innate immune system including complement factors and microglia/macrophage reactivity in the retina. Here, we show that lack of interferon-β signaling in the retina accelerates mononuclear phagocyte reactivity and promotes choroidal neovascularization (CNV) in the laser model of neovascular AMD Complete deletion of interferon-α/β receptor (Ifnar) using Ifnar1-/- mice significantly enhanced early microglia and macrophage activation in lesion areas. This triggered subsequent vascular leakage and CNV at later stages. Similar findings were obtained in laser-treated Cx3cr1Cre ER:Ifnar1fl/fl animals that allowed the tamoxifen-induced conditional depletion of Ifnar in resident mononuclear phagocytes only. Conversely, systemic IFN-β therapy of laser-treated wild-type animals effectively attenuated microgliosis and macrophage responses in the early stage of disease and significantly reduced CNV size in the late phase. Our results reveal a protective role of Ifnar signaling in retinal immune homeostasis and highlight a potential use for IFN-β therapy in the eye to limit chronic inflammation and pathological angiogenesis in AMD.

PMID: 27137488 [PubMed - as supplied by publisher]

Exp Eye Res. 2016 May 4. [Epub ahead of print]

A model of progressive photo-oxidative degeneration and inflammation in the pigmented C57BL/6J mouse retina.

Natoli R, Jiao H, Barnett NL, Fernando N, Valter K, Provis JM, Rutar M.

Abstract: Light-induced degeneration in rodent retinas is an established model for of retinal degeneration, including the roles of oxidative stress and neuroinflammatory activity. In these models, photoreceptor death is elicited via photo-oxidative stress, and is exacerbated by recruitment of subretinal macrophages and activation of immune pathways including complement propagation. Existing light damage models have relied heavily on albino rodents, and mostly using acute light stimuli. These albino models have proven valuable in uncovering the pathogenic mechanisms of such pathways in the context of retinal disease. However, their inherent albinism hinders comparability to normal retinal physiology, and also makes gene technology analyses time-consuming due to the predominance of the pigmented mouse strains in these applications. In this study, we characterise a new light damage model utilising C57BL/6J mice over a 7 day period of chronic light exposure. We use high-efficiency LED technology to deliver a sustained intensity of

100 k lux with negligible modulation of ambient temperature. We show that in the C57BL/6J mouse, chronic light exposure elicits the cardinal features of light damage including photoreceptor degeneration, atrophy of the choriocapillaris, decreased retinal function and increases in oxidative stress markers 4-HNE and 8-OHG, which emerge progressively over the 7 day period of exposure. These changes are accompanied by robust recruitment of IBA1+ and F4/80 + macrophages to the ONL and subretinal space, followed the strong up-regulation of monocyte-chemoattractants Ccl2, Ccl3, and Ccl12, as well as increases in expression of complement component C3. These findings are in agreement with prior damage models conducted in albino rodents such as Balb/c mice, and support the use of this new model in further investigating the causative features of oxidative stress and inflammation in retinal disease.

PMID: 27155143 [PubMed - as supplied by publisher]

Curr Mol Med. 2016 Apr 29. [Epub ahead of print]

Crosstalk between the autophagy-lysosome pathway and the ubiquitin-proteasome pathway in retinal pigment epithelial cells.

Zhan J, He J, Zhou Y, Wu M, Liu Y, Shang F, Zhang X.

BACKGROUND: The accumulation of damaged or misfolded proteins in retinal pigment epithelial (RPE) cells was considered a contributing factor for RPE dysfunction in age-related macular degeneration (AMD). The ubiquitin-proteasome pathway (UPP) and the autophagy-lysosome pathway (ALP) are the two major proteolytic systems for clearance of misfolded or damaged proteins.

OBJECTIVE: The aim is to investigate how these two systems communicate and coordinate with each other in RPE cells for eliminating intracellular misfolded and damaged proteins.

METHODS: Cultured ARPE-19 cells were treated with proteasome inhibitor MG132 and lysosomotropic agent chloroquine (CQ), respectively. The levels and cellular distributions of ubiquitinated proteins, LC3-I, LC3-Ⅱ, LAMP1 and p62 were analyzed by Western blotting and immunofluorescence. Proteasome activity was determined using Suc-LLVY-AMC as a substrate.

RESULTS: The level of ubiquitinated protein aggregations was significantly increased after the treatment of MG132 in RPE cells. The levels of LC3-I, LC3-II and LAMP1 increased in MG132 treated cells. The levels ofγ-tubulin and p62 also increased in MG132 treated cells, suggesting inhibition of the UPP up-regulates autophagy-lysosome pathway. Inhibition of lysosomal activity with CQ also increased the levels of high mass ubiquitin conjugates, LC3-II and p62. In addition, proteasome activity was compromised upon prolonged lysosomal inhibition.

CONCLUSIONS: These data indicate that the UPP and the ALP are interrelated and that dysfunction of the ALP would also result in dysfunction of the UPP and severely compromise the capacity of eliminating misfolded and other forms of damaged proteins.

PMID: 27132793 [PubMed - as supplied by publisher]

Free Radic Biol Med. 2016 May 2. [Epub ahead of print]

Protective effects of NSP-116, a novel imidazolyl aniline derivative, against light-induced retinal damage in vitro and in vivo.

Izawa H, Shimazawa M, Inoue Y, Uchida S, Moroe H, Tsuruma K, Hara H.

Abstract: In this study, we investigated the protective effects of NSP-116 [4-(4-acetylpiperazin-1-yl)-2-(1H-imidazol-1-yl) aniline], a novel imidazolyl aniline derivative, against light-induced photoreceptor cell

damage. In an in vitro experiment, murine photoreceptor (661W) cells were damaged by exposure to light for 24h. Viability of 661W cells after light exposure was assessed by Hoechst 33342/Propidium iodide nuclear staining and a tetrazolium salt (WST-8) assay. Intracellular radical production in 661W cells was evaluated using the reactive oxygen species (ROS) sensitive probe 5-(and 6)-chloromethyl-2, 7-dichlorodihydrofluorescein diacetate acetyl ester (CM-H2DCFDA). NSP-116 significantly suppressed light-induced cell death and ROS production in 661W cells. In an in vivo mouse experiment, retinal damage was induced by exposure to white light at 8,000lx for 3h after dark adaptation. Retinal damage was evaluated by recording the electroretinogram and measuring the outer nuclear layer (ONL) thickness at 5 days after light exposure. Single oral administration of NSP-116 before light exposure protected retinal function and ONL thinning after light exposure. Furthermore, the effect of NSP-116 on lipid peroxidation was evaluated using thiobarbituric acid reactive substance (TBARS) assay in porcine retina, and was found to decrease the production of TBARS. Electron spin resonance (ESR) measurements showed that NSP-116 exhibited radical scavenging activities against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, superoxide anion radical (·O2-), and hydroxyl radical (·OH). These findings suggest that NSP-116 has protective effects against light -induced photoreceptor degeneration in vitro and in vivo as a free radical scavenger, and it may be a novel therapeutic agent for retinal degenerative disorders, such as dry age-related macular degeneration (AMD).

PMID: 27151507 [PubMed - as supplied by publisher]

Epidemiology

Retina. 2016 May 3. [Epub ahead of print]

DOUBLE RETINAL PIGMENT EPITHELIUM TEARS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Mouallem A, Sarraf D, Chen X, Capuano V, Souied EH, Querques G.

PURPOSE: To describe the occurrence and treatment outcomes of double retinal pigment epithelium (RPE) tears in neovascular age-related macular degeneration and to elucidate the mechanism of tear development by means of multimodal imaging analysis.

METHODS: Fundus autofluorescence, spectral-domain optical coherence tomography, fluorescein angiography, and indocyanine green angiography were retrospectively studied before and after the occurrence of first and second RPE tears and at the final visit.

RESULTS: Twelve eyes of 10 patients that developed double RPE tears, either simultaneously (6 eyes) or at variable intervals after repeated intravitreal anti-vascular endothelial growth factor administration (6 eyes), were included. First RPE tears developed after a mean of 4.5 ± 2.7 anti-vascular endothelial growth factor injections; second RPE tears developed after a mean of 7.1 ± 5.2 anti-vascular endothelial growth factor injections. Mean best-corrected visual acuity was 20/63 at baseline evaluation, 20/76 after occurrence of first tear, 20/90 after occurrence of second tear, and 20/95 at final visit ($P > 0.05$ for all). Multimodal imaging revealed in all cases a Type 1 neovascular lesion adherent to the posterior surface of the RPE and spanning a significant portion of the pigment epithelium detachment with variable orientation; after development of double tears, the RPE seemed retracted on both borders of the neovascular network.

CONCLUSION: Double RPE tears may occur on opposite sides of a vascularized pigment epithelium detachment, in eyes with neovascular age-related macular degeneration after anti-vascular endothelial growth factor therapy, because of neovascular contraction of a Type 1 neovascular complex, adherent to the posterior surface of the RPE and spanning a significant portion of the pigment epithelium detachment area.

PMID: 27145251 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2016 May 6. [Epub ahead of print]

Age-related macular degeneration in patients with uveitis.

Fox AR, Chew EY, Meyerle C, Vitale S, Ferris FL, Nussenblatt RB, Sen HN.

PURPOSE: To evaluate the prevalence of large drusen in a uveitis clinic population.

DESIGN: Retrospective, cohort study.

METHODS: Patients with primary, non-infectious uveitis 55 years or older who were seen at the National Eye Institute of the National Institutes of Health from 2004 through August 2013 were reviewed using electronic medical records and photographic databases. Patients were classified as having age-related macular degeneration (AMD) if either eye had large drusen, geographic atrophy or neovascular AMD according to definitions used by the Eye Diseases Prevalence Research Group (EDPRG). The expected number of cases and standardised mortality ratio (SMR) for large drusen were estimated based on EDPRG estimates.

RESULTS: We identified 177 patients aged ≥55 years as having primary non-infectious uveitis; 170 (96.0%) had gradable fundus photos. Average age was 65.0±7.5 years (range 55-87), and 87 were non-Hispanic white, 66 non-Hispanic black, 6 Hispanic white and 11 of other race/ethnicity. Large drusen were identified in four patients (2.4%; 95% CI 0.6 to 6.0). No patients were identified to have late AMD. In the uveitis cohort, the SMR for cases of large drusen, which was adjusted for age, was calculated to be 0.32 (95% CI 0.12 to 0.70) for the whole cohort, 0.28 (95% CI 0.09 to 0.79) for non-Hispanic whites and 0.46 (95% CI 0.14 to 1.29) for non-Hispanic blacks.

CONCLUSIONS: Large drusen prevalence among patients with uveitis ≥55 years of age appears less than the prevalence in the general US population after accounting for differences in age distribution, especially for non-Hispanic whites. Although the racial and gender distribution in this study population is not directly representative of the general US population, results of this study suggest possible sparing of patients with uveitis from AMD. A larger systematic study with greater power would be needed to confirm these findings.

PMID: 27154918 [PubMed - as supplied by publisher]

Genetics

Invest Ophthalmol Vis Sci. 2016 May 1;57(6):2463-71.

Distinct Genetic Risk Profile of the Rapidly Progressing Diffuse-Trickling Subtype of Geographic Atrophy in Age-Related Macular Degeneration (AMD).

Fleckenstein M, Grassmann F, Lindner M, Pfau M, Czauderna J, Strunz T, von Strachwitz C, Schmitz-Valckenberg S, Holz FG, Weber BH.

PURPOSE: To genetically characterize a subphenotype of geographic atrophy (GA) in AMD associated with rapid progression and a diffuse-trickling appearance on fundus autofluorescence imaging.

METHODS: Patients from the Fundus Autofluorescence in Age-Related Macular Degeneration Study were phenotyped for diffuse-trickling GA (dt-GA; n = 44). DNA was analyzed for 10 known AMD-associated genetic variants. A genetic risk score (GRS) was calculated and compared with patients with nondiffuse-trickling GA (ndt-GA; n = 311) and individuals from the 1000 genomes project (1000G; n = 267). Given the phenotypic overlap between diffuse-trickling and late-onset retinal degeneration (LORD), all C1QTNF5 exons and their exon/intron boundaries were sequenced.

RESULTS: A statistically significant difference in allele frequencies between dt-GA and ndt-GA were found for CFH:rs1061170 and CFH:rs800292 (Pcorrected = 0.03). The ARMS2 variant rs10490924 was

significantly more frequent in dt-GA than in 1000G individuals (Pcorrected < 0.01). The GRS of dt-GA patients was in-between the score of the 1000G individuals and that of patients with ndt-GA, significantly differing from both (Pcorrected <0.01). Sequencing of C1QTNF5 revealed 28 unique variants although none showed a statistically significant association with dt-GA when compared with 1000G individuals.

CONCLUSIONS: The dt-GA phenotype shows a remarkably different genetic risk profile from other GA phenotypes secondary to AMD. Disease-associated C1QTNF5 mutations were not identified. Together, these results suggest that the dt-GA phenotype is associated with a genetic background substantially different from other GA phenotypes and underlines the necessity to refine the clinical phenotyping, specifically when aiming for individualized therapies in AMD.

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Association of the polymorphism Y402H in the CFH gene with response to anti-VEGF treatment in age-related macular degeneration: a systematic review and meta-analysis.

Hong N, Shen Y, Yu CY, Wang SQ, Tong JP.

Abstract: To explore whether the complement factor H (CFH) polymorphism rs1061170/Y402H is associated with responsiveness to antivascular endothelial growth factor (VEGF) agents in age-related macular degeneration (AMD). We reviewed the English literature to examine the association between the polymorphism rs1061170/Y402H of the CFH gene and responsiveness to treatment with anti-VEGF drugs in AMD patients. A meta-analysis of eligible studies was also performed. Pooled odds ratios (ORs) and 95% CIs were estimated using Stata V.12.0. Statistical heterogeneity was measured using Q-statistic testing. Fourteen relevant studies including a total of 2963 AMD patients were eligible. In AMD patients without a treatment history, individuals carrying the rs1061170/Y402H TT genotype were more likely to achieve a better outcome (OR = 1.932, 95% CI = 1.125-3.317, p = 0.017) than those carrying the CC genotype. The polymorphism rs1061170/Y402H might be a genetic predictor of treatment response to anti-VEGF therapy in AMD patients. Further prospective research including a larger number of patients is needed to validate this finding.

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Diet, lifestyle and low vision

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Changes in Visual Function in the Elderly Population in the United States: 1995-2010.

Chen Y, Hahn P, Sloan FA.

PURPOSE: To document recent trends in visual function among the United States population aged 70+ years and investigate how the trends can be explained by inter-temporal changes in: (1) population sociodemographic characteristics, and chronic disease prevalence, including eye diseases (compositional changes); and (2) effects of the above factors on visual function (structural changes).

METHODS: Data from the 1995 Asset and Health Dynamics among the Oldest Old (AHEAD) and the 2010 Health and Retirement Study (HRS) were merged with Medicare Part B claims in the interview years and the 2 previous years. Decomposition analysis was performed. Respondents from both studies were aged 70+ years. The outcome measure was respondent self-reported visual function on a 6-point scale (from 6 = blind to 1 = excellent).

RESULTS: Overall, visual function improved from slightly worse than good (3.14) in 1995 to slightly better than good (2.98) in 2010. A decline in adverse effects of aging on vision was found. Among the compositional changes were higher educational attainment leading to improved vision, and higher prevalence of such diseases as diabetes mellitus, which tended to lower visual function. However, compared to compositional changes, structural changes were far more important, including decreased adverse effects of aging, diabetes mellitus (when not controlling for eye diseases), and diagnosed glaucoma.

CONCLUSION: Although the US population has aged and is expected to age further, visual function improved among elderly persons, especially among persons 80+ years, likely reflecting a favorable role of structural changes identified in this study in mitigating the adverse effect of ongoing aging on vision.

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[Localization of scotomas in AMD by reading test : Random series of words in standardized format]. [Article in German]

Eisenbarth W, Pado U, Schriever S, Schötschel D, Feucht N, MacKeben M.

BACKGROUND: Reading performance that can be measured by reading tests depends on whether reading material with or without contextual continuity is used.

OBJECTIVE: The goal of this study was to create a German version of the SKread test and to evaluate it in a clinical setting.

MATERIAL AND METHODS: The evaluation of the SKread test was first performed on two groups of visually healthy subjects of different ages: a junior group of 25 persons with ages between 20 and 30 years (mean = 25.84 years, SD ± 2.41 years) and a senior group of 25 persons with ages between 51 and 84 years (mean = 62.40 ± 8.46 years). The same measurements were also performed on a group of 18 patients with age-related macular degeneration (AMD) with ages between 75 and 95 years (mean = 81.89 ± 5.48 years). The reading performance was also measured using Radner charts.

RESULTS: Using reading material without syntactic continuity considerably slowed down the reading speed and increased the error rate. Median reading rates of 11.53 characters/s (CPS) for the junior group and 8.96 CPS for the senior group were clearly lower than those for the Radner charts (22.02 CPS and 18.48 CPS, respectively). In the AMD patients, a statistical analysis of the error rates showed a highly significant difference between the Radner charts and the SKread test ($p = 0.00014$). Furthermore, by analyzing the errors made in the SKread test information could be obtained about the position of central scotomas. The test-retest reliability of the SKread was very good.

CONCLUSION: Information about the position of a central scotoma can be acquired by using the SKread test and an analysis of reading errors, which can augment effective clinical monitoring in AMD and subsequent visual rehabilitation.

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