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Drug treatment

J Ophthalmol. 2011;2011:742020. Epub 2011 Jun 12.

Early responses to intravitreal ranibizumab in typical neovascular age-related macular degeneration and polypoidal choroidal vasculopathy.

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Purpose: To evaluate the early response to intravitreal ranibizumab (IVR) in two different phenotypes of age-related macular degenerations (AMD): typical neovascular AMD (tAMD) and polypoidal choroidal vasculopathy (PCV).

Methods: Sixty eyes from 60 patients (tAMD 28, PCV 32 eyes) were recruited. Three consecutive IVR treatments (0.5 mg) were performed every month. Change in the best-corrected visual acuity (BCVA) and central retinal thickness (CRT) was then compared between the tAMD and PCV groups.

Results: The mean BCVA logMAR was significantly improved at month 1 and month 3 after the initial IVR in the tAMD group, but there was no change in the PCV group. Both phenotypes showed significant improvements in the CRT during the 3 months after the initial IVR. There were no significant differences in the improvements of the CRT in the tAMD versus the PCV group. In the stepwise analysis, a worse pretreatment BCVA and tAMD lesions were significantly beneficial for a greater improvement of BCVA at 3 months after the initial IVR.

Conclusions: The phenotype of tAMD showed a significantly better early response to IVR than PCV in terms of BCVA improvement.

PMID: 21772985 [PubMed - in process]

J Ophthalmol. 2011;2011:159436. Epub 2011 Jun 16.

Prophylaxis of macular edema with intravitreal ranibizumab in patients with diabetic retinopathy after cataract surgery: a pilot study.

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Abstract

The purpose of this study was to evaluate the effectiveness of intravitreal ranibizumab (Lucentis, Genentech, South San Francisco, Calif, USA) combined with cataract surgery for the prevention of clinically significant macular edema (CSME) in patients with diabetic retinopathy (DR). This prospective interventional case series included fifty-four eyes of 54 patients with a previous diagnosis of nonproliferative diabetic retinopathy (NPDR) without macular edema preoperatively. Subjects were assigned in a 1 : 1 ratio to receive an intraoperative intravitreal ranibizumab injection (n = 27) or not (control group, n = 27) associated with standardised phacoemulsification surgery. The main outcome measure was the incidence of CSME one and three months after surgery. One month after surgery the incidence of CSME in the control group was 25.92% and 3.70% in the treatment group and at three months was 22.22% and 3.70%, respectively. Short-term results suggest that intravitreal ranibizumab immediately after phacoemulsification prevents CSME in patients with NPDR.

PMID: 21772983 [PubMed - in process]

Other treatment & diagnosis

Prog Brain Res. 2011;192:199-262.

Vision restoration after brain and retina damage: The "residual vision activation theory".

Sabel BA, Henrich-Noack P, Fedorov A, Gall C.

Abstract

Vision loss after retinal or cerebral visual injury (CVI) was long considered to be irreversible. However, there is considerable potential for vision restoration and recovery even in adulthood. Here, we propose the "residual vision activation theory" of how visual functions can be reactivated and restored. CVI is usually not complete, but some structures are typically spared by the damage. They include (i) areas of partial damage at the visual field border, (ii) "islands" of surviving tissue inside the blind field, (iii) extrastriate pathways unaffected by the damage, and (iv) downstream, higher-level neuronal networks. However, residual structures have a triple handicap to be fully functional: (i) fewer neurons, (ii) lack of sufficient attentional resources because of the dominant intact hemisphere caused by excitation/inhibition dysbalance, and (iii) disturbance in their temporal processing. Because of this resulting activation loss, residual structures are unable to contribute much to everyday vision, and their "non-use" further impairs synaptic strength. However, residual structures can be reactivated by engaging them in repetitive stimulation by different means: (i) visual experience, (ii) visual training, or (iii) noninvasive electrical brain current stimulation. These methods lead to strengthening of synaptic transmission and synchronization of partially damaged structures (within-systems plasticity) and downstream neuronal networks (network plasticity). Just as in normal perceptual learning, synaptic plasticity can improve vision and lead to vision restoration. This can be induced at any time after the lesion, at all ages and in all types of visual field impairments after retinal or brain damage (stroke, neurotrauma, glaucoma, amblyopia, age-related macular degeneration). If and to what extent vision restoration can be achieved is a function of the amount of residual tissue and its activation state. However, sustained improvements require repetitive stimulation which, depending on the method, may take days (noninvasive brain stimulation) or months (behavioral training). By becoming again engaged in everyday vision, (re) activation of areas of residual vision outlasts the stimulation period, thus contributing to lasting vision restoration and improvements in quality of life.

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Br J Ophthalmol. 2011 Jul 18. [Epub ahead of print]

Subjective and functional deterioration in recurrences of neovascular AMD are often preceded by morphologic changes in optic coherence tomography.

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Abstract

Background Different tests were applied to test the sensitivity of patient self-control; Amsler grid and visual acuity (VA) assessment, as well as fundus examinations to reveal recurrent choroidal neovascularisation (CNV) activity in age-related macular degeneration as detected by spectral domain optical coherence tomography (SD-OCT) in monthly controls. **Methods** A prospective interventional case series of patients with exudative age-related macular degeneration was examined, which received ranibizumab injections until complete resolution of fluid in SD-OCT. Analysis of changes in subjective perception, Amsler grid, early treatment diabetic retinopathy study (ETDRS) VA, Radner reading VA and fundus examination was conducted in the case of OCT-confirmed CNV recurrences. **Results** Out of 40 morphological recurrences determined by SD-OCT, six (15%) were noticed by subjective patient perception. Amsler grid testing revealed deterioration in 12 cases (30%); 11 recurrences (28%) were accompanied by loss of ≥ 5 letters in ETDRS VA and/or ≥ 1 line in Radner VA; fundus examination showed signs of novel CNV activity in 10 out of 40 recurrences (25%). The combined sensitivity of all diagnostic methods compared to SD-OCT for recurrence detection was 67.5% (27 out of 40 recurrences). **Conclusion** Subjective patient perception, Amsler grid, VA as well as fundus examination lead to pronounced underestimations of CNV recurrences. Morphologic recurrences can be detected prior to functional deterioration. As any delay of treatment can result in irreversible vision loss, attempts should be made to provide monthly OCT controls to detect recurrences as early as possible.

PMID: 21768186 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2011 Jul 15. [Epub ahead of print]

Feasibility of a Method for En Face Imaging of Photoreceptor Cell Integrity.

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PURPOSE: To report a method for en face imaging of the photoreceptor inner and outer segment junction by spectral-domain optical coherence tomography (SD OCT) and to describe findings in normal subjects and patients with various retinal diseases.

DESIGN: Observational case series.

METHODS: SD OCT images were acquired from 6 normal subjects (mean age, 44 ± 11 years) and from 5 subjects with retinal diseases (mean age, 66 ± 22 years). A customized high-density SD OCT volume scan was acquired on the retina. SD OCT B-scan images were segmented automatically to extract intensity data along the inner and outer segment junction. Data obtained from the raster B-scans were combined to generate an inner and outer segment en face image in a 4.4×4.4 -mm retinal area centered on the fovea. The foveal-to-parafoveal mean intensity ratio was measured, and repeatability was determined. An infrared scanning laser ophthalmoscope image was acquired and was cropped to provide a field of view similar to the inner and outer segment en face image.

RESULTS: Inner and outer segment en face images generated in normal subjects provided clear visualization of the retinal vasculature, matching the vascular network observed in the infrared scanning laser oph-

thalmoscope image. In normal subjects, the foveal-to-parafoveal mean intensity ratio was 0.88 ± 0.06 , and repeatability of measurements was, on average, 7%. In macular hole, a dark circular region was observed in the inner and outer segment en face image, indicative of photoreceptor cell loss. In age-related macular degeneration, the en face image displayed nonuniform texture corresponding to topographic variations in the inner and outer segment junction. In central serous retinopathy, areas of lower intensity were visible on the en face image corresponding to regions of prior neurosensory elevation. In cystoid macular edema, reduced intensity was present in the inner and outer segment en face image in areas with increased retinal thickness. In diabetic retinopathy, the inner and outer segment en face image displayed regions of reduced intensity resulting from edema, laser scars, or both.

CONCLUSIONS: Detection of intensity abnormalities in the inner and outer segment en face image is useful for monitoring the integrity of photoreceptor cells in the course of disease progression and therapeutic intervention.

PMID: 21764030 [PubMed - as supplied by publisher]

Retina. 2011 Jul 19. [Epub ahead of print]

RECOVERY OF THE NEUROSENSORY RETINA AFTER MACULAR TRANSLOCATION SURGERY IS INDEPENDENT OF PREOPERATIVE MACULAR SENSITIVITY IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To directly assess the recovery of the retina overlying choroidal neovascularization in neovascular age-related macular degeneration and to understand the relationship between macular sensitivity and visual functional measures and retinal structural alterations as predictive factors for outcome among eyes undergoing macular translocation surgery (MT360).

METHODS: In a prospective, consecutive case series of 55 patients with subfoveal choroidal neovascularization undergoing MT360, we explored the relationship between macular sensitivity on the Nidek microp-erimeter-1 with pathologic features on optical coherence tomography and with distance and near visual acuity, reading speed, contrast sensitivity, color vision, and National Eye Institute Visual Function Question-naire-25 composite quality-of-life (QOL) score, both before and at 1 year after MT360.

RESULTS: On average, there was improvement in all measures of visual function, macular sensitivity, and QOL after MT360. Preoperative median retinal sensitivity score did not predict postoperative measures of visual function, macular sensitivity, and vision-related QOL. Correlation between preoperative median retinal sensitivity score and preoperative measures of visual function and vision-related QOL was generally poor, excepting modest correlation for contrast sensitivity and color vision. However, correlation between postoperative median retinal sensitivity score and postoperative measures of visual function and vision-related QOL was uniformly modest, and change in median retinal sensitivity score correlated modestly with change in most measures of visual function and QOL. Among optical coherence tomography morphologic features, preoperative retinal pigment epithelium elevation predicted reduced postoperative contrast sensitivity ($P = 0.04$), while preoperative epiretinal membrane or vitreomacular traction predicted increased postoperative contrast sensitivity ($P = 0.05$). Preoperative cystoid macular edema, subretinal fluid, and subretinal lesion were associated with decreased median retinal sensitivity score (P values ≤ 0.03).

CONCLUSION: Our findings demonstrate the resilience and recovery of poorly functioning retina in neovascular age-related macular degeneration but fail to demonstrate a role for macular sensitivity as measured by Nidek microperimeter-1 in identifying irreversibly damaged retina that would not benefit from MT360.

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Epidemiology & pathogenesis

Invest Ophthalmol Vis Sci. 2011 Jul 21. [Epub ahead of print]

Rates of Nonexudative and Exudative Age-Related Macular Degeneration Among Asian-American Ethnic Groups.

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Objective: To determine whether the risk of developing nonexudative and exudative age-related macular degeneration (AMD) varies for Americans of different Asian ethnicities.

Methods: Claims data from a large, national United States (U.S.) managed care network were reviewed to identify Asian Americans age ≥ 40 who had ≥ 1 eye care visits from 2001-2007. International Classification of Disease (ICD-9CM) billing codes were used to identify enrollees with nonexudative and exudative AMD. Incidence and prevalence rates were calculated for non-exudative and exudative AMD and stratified by Asian ethnicity. Cox regression analyses were performed to determine the relative hazards of developing nonexudative and exudative AMD for individuals of different Asian ethnicities, with adjustment for sociodemographic factors, ocular and medical conditions.

Results: Of the 44,103 Asian Americans who met the inclusion criteria, 2,221 (5.04%) had nonexudative AMD and 217 (0.49%) had exudative AMD. Chinese Americans (adjusted hazard ratio (HR)=1.63, confidence interval (CI) 1.50-1.77) and Pakistani Americans (HR=1.97, CI 1.40-2.77) had a significantly increased hazard of developing nonexudative AMD compared with non-Hispanic whites. By contrast, Japanese Americans had a 29% decreased hazard of nonexudative AMD compared with whites (HR=0.71, CI 0.59-0.85). There were no significant differences in hazards for developing exudative AMD for any of the Asian ethnicities relative to whites.

Conclusion: Asian Americans are the second fastest growing racial group within the U.S. Eye care providers need to be aware of the overall disease burden of AMD within this group and appreciate how disease rates can vary substantially between different Asian ethnicities.

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J Oncol. 2011;2011:693424. Epub 2011 Apr 28.

From smoking to cancers: novel targets to neuronal nicotinic acetylcholine receptors.

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Abstract

Cigarette smoking bears a strong etiological association with many neovascularization-related diseases, including cancer, cardiovascular disease, and age-related macular degeneration. Cigarette smoke is a complex mixture of many compounds, including nicotine, which is the major active and addictive component of tobacco. Nicotine and its specific metabolized carcinogens directly bind to nicotinic acetylcholine receptors (nAChRs) on cell membranes and trigger the nAChR signal cascade. The nAChRs were originally thought to be ligand-gated ion channels that modulate physiological processes ranging from neurotransmission to cancer signaling. For several decades, the nAChRs served as a prototypic molecule for neurotransmitter receptors; however, they are now important therapeutic targets for various diseases, including Alzheimer's and Parkinson's diseases, schizophrenia, and even cancer. This paper describes recent advances in our understanding of the assembly, activity, and biological functions of nicotinic receptors,

as well as developments in the therapeutic application of nicotinic receptor ligands.

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Photochem Photobiol. 2011 Jul 19. doi: 10.1111/j.1751-1097.2011.00977.x. [Epub ahead of print]

Ultraviolet Light-Induced Cyclobutane Pyrimidine Dimers in Rabbit Eyes.

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Abstract

Sunlight exposure of the eye leads to pathologies including photokeratitis, cortical cataracts, pterygium, actinic conjunctivitis and age-related macular degeneration. It is well established that exposure to ultraviolet (UV) radiations lead to DNA damage, mainly cyclobutane pyrimidine dimers (CPDs). CPD formation is the principal factor involved in skin cancer. However, the exact mechanism by which sunlight induces ocular pathologies is not well understood. To shed light on this issue, we quantified the CPD formation onto DNA of rabbit ocular cells following UVB exposure. We found that CPDs were induced only in the ocular structures of the anterior chamber (cornea, iris and lens) and were more concentrated in the corneal epithelium. Residual UVB that pass through the cornea are completely absorbed by the anterior layers of the iris. CPDs were also detected in the central portion of the lens that is not protected by the iris (pupil). By determining the UV-induced DNA damage formation in eyes, we showed that anterior ocular structures are a reliable physical barrier that protects the subjacent structures from the toxic effects of UV. Although the corneal epithelium is the structure where most of the CPDs were detected, no cancer is related to solar exposure.

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Genetics

J Transl Med. 2011 Jul 15;9(1):111. [Epub ahead of print]

Complement Component C5a Promotes Expression of IL-22 and IL-17 from Human T cells and its Implication in Age-related Macular Degeneration.

Liu B, Wei L, Meyerle C, Tuo J, Sen HN, Li Z, Chakrabarty S, Agron E, Chan CC, Klein ML, Chew E, Ferris F, Nussenblatt RB.

BACKGROUND: Age related macular degeneration (AMD) is the leading cause of irreversible blindness in elderly populations worldwide. Inflammation, among many factors, has been suggested to play an important role in AMD pathogenesis. Recent studies have demonstrated a strong genetic association between AMD and complement factor H (CFH), the down-regulatory factor of complement activation. Elevated levels of complement activating molecules including complement component 5a (C5a) have been found in the serum of AMD patients. Our aim is to study whether C5a can impact human T cells and its implication in AMD.

METHODS: Human peripheral blood mononuclear cells (PBMCs) were isolated from the blood of exudative form of AMD patients using a Ficoll gradient centrifugation protocol. Intracellular staining and enzyme-linked immunosorbent assays were used to measure protein expression. Apoptotic cells were detected by staining of cells with the annexin-V and TUNEL technology and analyzed by a FACS Caliber flow cytometer. SNP genotyping was analyzed by TaqMan genotyping assay using the Real-time PCR system 7500.

RESULTS: We show that C5a promotes interleukin (IL)-22 and IL-17 expression by human CD4+ T cells. This effect is dependent on B7, IL-1beta and IL-6 expression from monocytes. We have also found that

C5a could protect human CD4+ cells from undergoing apoptosis. Importantly, consistent with a role of C5a in promoting IL-22 and IL-17 expression, significant elevation in IL-22 and IL-17 levels was found in AMD patients as compared to non-AMD controls.

CONCLUSIONS: Our results support the notion that C5a may be one of the factors contributing to the elevated serum IL-22 and IL-17 levels in AMD patients. The possible involvement of IL-22 and IL-17 in the inflammation that contributes to AMD may herald a new approach to treat AMD.

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Curr Med Res Opin. 2011 Jul 22. [Epub ahead of print]

The challenge of predicting macular degeneration.

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Abstract

This commentary critically evaluates the limitations of genetic risk predictions in multifactorial disease, with specific reference to age-related macular degeneration (AMD). AMD is a common blinding disease with 33 million people worldwide experiencing vision impairment. Although gene polymorphism combinations infer an up to 50-fold increased risk of developing the disease, we are far from predicting AMD based on genetics. In the case of complex multifactorial disease such as AMD, to have the same predictive certainty that exists for monogenic disorders, we must account for all gene-environment interactions. We discuss sensitive vision tests that reflect causal gene-environment mechanisms and their potential in AMD risk prediction.

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Pre-clinical

Am J Pathol. 2011 Jul 14. [Epub ahead of print]

Minocycline Attenuates Photoreceptor Degeneration in a Mouse Model of Subretinal Hemorrhage: Microglial Inhibition as a Potential Therapeutic Strategy.

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Abstract

Hemorrhage under the neural retina (subretinal hemorrhage) can occur in the context of age-related macular degeneration and induce subsequent photoreceptor cell death and permanent vision loss. Current treatments with the objective of removing or displacing the hemorrhage are invasive and of mixed efficacy. We created a mouse model of subretinal hemorrhage to characterize the inflammatory responses and photoreceptor degeneration that occur in the acute aftermath of hemorrhage. It was observed that microglial infiltration into the outer retina commences as early as 6 hours after hemorrhage. Inflammatory cells progressively accumulate in the outer nuclear layer concurrently with photoreceptor degeneration and apoptosis. Administration of minocycline, an inhibitor of microglial activation, decreased microglial expression of chemotactic cytokines in vitro and reduced microglial infiltration and photoreceptor cell loss after subretinal hemorrhage in vivo. Inflammatory responses and photoreceptor atrophy occurred after subretinal hemor-

rhage, however, the degree of response and atrophy were similar between C3-deficient and C3-sufficient mice, indicating a limited role for complement-mediated processes. Our data indicate a role for inflammatory responses in driving photoreceptor cell loss in subretinal hemorrhage, and it is proposed that microglial inhibition may be beneficial in the treatment of subretinal hemorrhage.

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Diet

PLoS One. 2011;6(7):e21926. Epub 2011 Jul 14.

Orally active multi-functional antioxidants are neuroprotective in a rat model of light-induced retinal damage.

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BACKGROUND: Progression of age-related macular degeneration has been linked to iron dysregulation and oxidative stress that induce apoptosis of neural retinal cells. Since both antioxidants and chelating agents have been reported to reduce the progression of retinal lesions associated with AMD in experimental animals, the present study evaluates the ability of multi-functional antioxidants containing functional groups that can independently chelate redox metals and quench free radicals to protect the retina against light-induced retinal degeneration, a rat model of dry atrophic AMD.

METHODS/RESULTS: Proof of concept studies were conducted to evaluate the ability of 4-(5-hydroxypyrimidin-2-yl)-N,N-dimethyl-3,5-dioxopiperazine-1-sulfonamide (compound 4) and 4-(5-hydroxy-4,6-dimethoxypyrimidin-2-yl)-N,N-dimethyl-3,5-dioxopiperazine-1-sulfonamide (compound 8) to reduce retinal damage in 2-week dark adapted Wistar rats exposed to 1000 lx of light for 3 hours. Assessment of the oxidative stress markers 4-hydroxynonenal and nitrotyrosine modified proteins and Thioredoxin by ELISA and Western blots indicated that these compounds reduced the oxidative insult caused by light exposure. The beneficial antioxidant effects of these compounds in providing significant functional and structural protection were confirmed by electroretinography and quantitative histology of the retina.

CONCLUSIONS/SIGNIFICANCE: The present study suggests that multi-functional compounds may be effective candidates for preventive therapy of AMD.

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