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Drug treatment

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Risk of Scar in the Comparison of Age-related Macular Degeneration Treatments Trials.

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OBJECTIVE: To describe risk factors for scar in eyes treated with ranibizumab or bevacizumab for neovascular age-related macular degeneration (AMD).

DESIGN: Prospective cohort study within a randomized clinical trial.

PARTICIPANTS: Patients with no scar on color fundus photography (CFP) or fluorescein angiography (FA) at enrollment in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

METHODS: Eyes were assigned to ranibizumab or bevacizumab treatment and to 1 of 3 dosing regimens for 2 years. Masked readers assessed CFP and FA. Baseline demographic characteristics, visual acuity, morphologic features on photography and optical coherence tomography (OCT), and genotypes associated with AMD risk were evaluated as risk factors using adjusted hazard ratios (aHRs) and associated 95% confidence intervals (CIs). Scars were classified as fibrotic with well-demarcated elevated mounds of yellowish white tissue or nonfibrotic with discrete flat areas of hyperpigmentation with varying amounts of central depigmentation.

MAIN OUTCOME MEASURES: Scar formation.

RESULTS: Scar developed in 480 of 1059 eyes (45.3%) by 2 years. Baseline characteristics associated with greater risk of scarring were predominantly classic choroidal neovascularization (CNV) (aHR, 3.1; CI, 2.4-3.9) versus occult CNV, blocked fluorescence (aHR, 1.4; CI, 1.1-1.8), foveal retinal thickness >212 μm (aHR, 2.4; CI, 1.7-3.6) versus <120 μm, foveal subretinal tissue complex thickness >275 μm (aHR, 2.4; CI, 1.7-3.6) versus ≤75 μm, foveal subretinal fluid (aHR, 1.5; CI, 1.1-2.0) versus no subretinal fluid, and subretinal hyperreflective material (SHRM) (aHR, 1.7; CI, 1.3-2.3) versus no SHRM. Eyes with elevation of the retinal pigment epithelium had lower risk (aHR, 0.6; CI, 0.5-0.8) versus no elevation. Drug, dosing regimen, and genotype had no statistically significant association with scarring. Fibrotic scars developed in 24.7% of eyes, and nonfibrotic scars developed in 20.6% of eyes. Baseline risk factors for the scar types were similar except that eyes with larger lesion size or visual acuity <20/40 were more likely to develop

fibrotic scars.

CONCLUSIONS: Approximately half of eyes enrolled in CATT developed scar by 2 years. Eyes with classic neovascularization, a thicker retina, and more fluid or material under the foveal center of the retina are more likely to develop scar.

PMID: 24314839 [PubMed - as supplied by publisher]

Biomed Res Int. 2013;2013:830837. Epub 2013 Nov 11.

Therapies for Neovascular Age-Related Macular Degeneration: Current Approaches and Pharmacologic Agents in Development.

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Abstract: As one of the leading causes of blindness, age-related macular degeneration (AMD) has remained at the epicenter of clinical research in ophthalmology. During the past decade, focus of researchers has ranged from understanding the role of vascular endothelial growth factor (VEGF) in the angiogenic cascades to developing new therapies for retinal vascular diseases. Anti-VEGF agents such as ranibizumab and aflibercept are becoming increasingly well-established therapies and have replaced earlier approaches such as laser photocoagulation or photodynamic therapy. Many other new therapeutic agents, which are in the early phase clinical trials, have shown promising results. The purpose of this paper is to briefly review the available treatment modalities for neovascular AMD and then focus on promising new therapies that are currently in various stages of development.

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J Ophthalmol. 2013;2013:786107. Epub 2013 Nov 11.

Is Spectral-Domain Optical Coherence Tomography Essential for Flexible Treatment Regimens with Ranibizumab for Neovascular Age-Related Macular Degeneration?

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Purpose: To evaluate the ability of spectral-domain optical coherence tomography to detect subtle amounts of retinal fluid when the choroidal neovascularization is detected as inactive via time-domain optical coherence tomography and clinical examination in neovascular age-related macular degeneration (nAMD) patients.

Methods: Forty-nine eyes of 49 patients with nAMD after ranibizumab treatment were included in this cross-sectional, prospective study. All patients were imaged with TD-OCT and SD-OCT at the same visit one month after a ranibizumab injection. The presence of subretinal, intraretinal, and subretinal pigment epithelium fluid (subRPE) in SD-OCT was evaluated; also mean central retinal thickness (CRT) and the rate of vitreoretinal surface disorders detected via the two devices were evaluated.

Results: The mean CRT via TD-OCT and SD-OCT was 218.1 ± 51.3 and 325.7 ± 78.8 microns. Sixteen patients (32.6%) showed any kind of retinal fluid via SD-OCT. In detail, 8 patients (16.3%) showed

subretinal fluid, 10 patients (20.4%) showed intraretinal fluid, and 3 patients (6.1%) showed SubRPE fluid. The ability of detecting vitreoretinal surface disorders was comparable between the two devices, except vitreomacular traction.

Conclusion: SD-OCT is essential for the nAMD patients who are on an as-needed treatment regimen with ranibizumab. Only TD-OCT and clinical examination may cause insufficient treatment in this group of patients.

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Other treatment & diagnosis

Microvasc Res. 2013 Dec 5. pii: S0026-2862(13)00201-X. doi: 10.1016/j.mvr.2013.11.005. [Epub ahead of print]

Objective area measurement technique for choroidal neovascularization from fluorescein angiography.

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Abstract: The purpose of this study was to develop a non-biased method of quantitatively measuring choroidal neovascularization (CNV) areas based on late-phase fluorescein angiography (FA) images. Experimental CNV was induced in Long Evans rats by laser disruption of the Bruch's membrane. FA was performed weekly for 5weeks. Multi-Otsu thresholding (MOT) was used to quantify CNV in late-phase FA images from both experimental rodent CNV and wet age-related macular degeneration (wAMD) patients. Images were automatically thresholded into three levels based on the image histogram, with the highest level containing CNV. To determine the technique's ability to quantify CNV areas, rats were given either triamcinolone acetonide or dexamethasone sodium phosphate to treat CNV and compared to untreated rats. The rat CNV lesion areas measured from 5-week histology sections from each treatment group were compared to areas measured from the corresponding FA images. MOT was able to detect statistical decreases in rodent CNV area in the treatment groups versus control from weeks 3 through 5. The ratio of CNV area measured from histology to area measured from FA images was not statistically different between groups. Finally, to determine the usefulness of MOT on pathological morphologies of CNV, MOT was performed on late-phase FA images from patients with classic and diffuse CNV. The technique was able to segment classical CNV in wAMD patients, but performed poorly with diffuse CNV. MOT provides a robust, objective, and quantifiable area measurement of CNV lesion area in both experimentally-induced and pathological CNV. The results indicate that MOT could be a useful research tool in helping evaluate the effects of therapeutics on CNV growth.

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Jpn J Ophthalmol. 2013 Dec 12. [Epub ahead of print]

Multimodal evaluation of macular function in age-related macular degeneration.

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OBJECTIVE: To evaluate macular function using multimodality in eyes with age-related macular degeneration (AMD) at various stages.

METHODS: Macular function in 20 control eyes (20 subjects), 17 eyes (17 patients) with large drusen, 18 eyes (18 patients) with drusenoid pigment epithelial detachment (PED), and 19 eyes (19 patients) with neovascular AMD was examined using a Landolt chart for visual acuity; retinal sensitivity was measured by microperimetry; and focal macular electroretinography (fmERG) was performed. In all of these eyes, retinal morphology was examined using optical coherence tomography.

RESULTS: Eyes with neovascular AMD showed morphologic changes in the neurosensory retina as well as marked deterioration of macular function in all parameters measured with a Landolt chart, fmERG, and microperimetry. Eyes with large drusen showed only minimal morphologic changes in the neurosensory retina. In this large drusen group, although retinal sensitivity at the central point was significantly decreased ($P = 0.0063$), the other parameters of macular function were well preserved. In eyes with drusenoid PED, the structure of the neurosensory retina was well preserved, while the foveal thickness was significantly increased ($P = 0.013$). The macular function of these eyes was significantly deteriorated, with the VA, amplitude of the a-wave and b-wave, and retinal sensitivity being markedly decreased. In addition, the area of PED correlated with the latency of the a-wave and b-wave and with the retinal sensitivity within the central 4° or 8° region.

CONCLUSION: Multimodal evaluation demonstrated a significant decrease in macular function in drusenoid PED and in neovascular AMD.

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Am J Ophthalmol. 2013 Sep 29. pii: S0002-9394(13)00648-X. doi: 10.1016/j.ajo.2013.09.026. [Epub ahead of print]

Increased Risk of Parkinson Disease Following a Diagnosis of Neovascular Age-Related Macular Degeneration: A Retrospective Cohort Study.

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PURPOSE: To investigate the risk for Parkinson disease during a 3-year follow-up period after a diagnosis of neovascular age-related macular degeneration (AMD) using a nationwide population-based dataset in Taiwan.

DESIGN: A retrospective matched-cohort study.

METHODS: We identified 877subjects with neovascular AMD as the study cohort and randomly selected 8770 subjects for a comparison cohort. Each subject was individually followed for a 3-year period to identify those who subsequently developed Parkinson disease. Stratified Cox proportional hazard regressions were performed as a means of comparing the 3-year risk of subsequent Parkinson disease between the study and comparison cohorts.

RESULTS: The incidence rate of Parkinson disease was 5.32 (95% confidence interval [CI]: 3.03-8.72) per 1000 person-years in patients with neovascular AMD and 2.09 (95% CI: 1.59-2.70) per 1000 person-years in comparison patients. The log-rank test indicated that subjects with neovascular AMD had a significantly lower 3-year Parkinson disease-free survival rate than comparison subjects ($P < .001$). After censoring cases in which patients died during the follow-up period and adjusting for monthly income, geographic region, hypertension, diabetes, hyperlipidemia, and coronary heart disease, the hazard ratio of Parkinson disease during the 3-year follow-up period for subjects with neovascular AMD was 2.57 (95% CI: 1.42-4.64) that of comparison subjects.

CONCLUSION: In this study, subjects with neovascular AMD were found to be at a significant risk of Parkinson disease during a 3-year follow-up period after their diagnosis among Taiwanese Chinese. Further study is needed to confirm our findings and explore the underlying pathomechanism.

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Pathogenesis

Bull Acad Natl Med. 2012 Nov;196(8):1587-98; discussion 1598.

[Role of defective intracellular proteolysis in human degenerative diseases].[Article in French]

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Abstract: Although intracellular protein synthesis has been studied extensively, protein degradation and disposal, know as proteolysis, has been relatively neglected. Modern studies which led two Nobel prizes (de Duve in 1950 and Herschko, Rose and Ciechanover in 1980) established that proteolysis is ensured by two separate but complementary mechanisms: lysosomes responsible for auto and heterophagy and the Ubiquitin-Proteasome System (UPS). The UPS involves ubiquitin, a small molecule consisting of 76 amino acids found in all eukaryotic cells that ensures the identification of the protein to be degraded and its transport to the proteasome, an intracellular complex with enzymes which degrade unneeded or damaged proteins. The proteasome, acting as a composting agent, ensures the enzymatic dissociation of the protein. In this degradation process, as infinite screw, ubiquitin, peptides and amino acids are released and made available for a new cycle. Knowledge of the UPS and its related disorders is continually expanding. Concurrent with lysosomes which work in acidic environment, it is currently known that the UPS provides 80% to 90% of the proteolysis of the short-life proteins and ensures, as chaperon-molecules, the right conformation and hence the correct function of the proteins. The proteolytic activity generates abnormal residues (tau protein, amyloid and related proteins) and various soluble and insoluble wastes. Some are precipitated as inclusion-bodies or aggregosomes, identified years ago by pathologists. These aggregosomes affect almost exclusively long-lived cells (nervous and muscular, macophages). Pigment deposits, such as lipofuscines made by the peroxydation of cell membranes, are the most abundant. Due to their diverse chemical composition, they cannot be empoyed for a scientific classification. Failures of these systems are numerous. They vary not according to the chemical nature of the abnormal protein and wastes but the life span of the targeted cells and the nature of proteolysis. In this article, therefore, the following distinction should be made:--Lysosomal failures. They represent hereditary metabolic disorders involving all categories of cells. They are characterized by the accumulation of homogeneous material related to the underlying disease. Young people are predominantly affected--UPS failures. They represent sporadic conditions principally involving long-lived cells. The accumulated material is heterogeneous, composed of abnormal proteins and various "garbage-like" waste, including pigments. The elderly are predominatly affected, suggesting an epigenetic wear and tear process. Hypothetically, most the sporadic neurodegenerative diseases, from retinal macular degeneration and its associated drüsen to Alzheimer's disease, Parkinson's disease may represent fairly good examples of the UPS deficit.

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Essential Role of Thioredoxin 2 in Mitigating Oxidative Stress in Retinal Epithelial Cells.

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Abstract: The retina is constantly subjected to oxidative stress, which is countered by potent antioxidative systems present in retinal pigment epithelial (RPE) cells. Disruption of these systems leads to the development of age-related macular degeneration. Thioredoxin 2 (Trx2) is a potent antioxidant, which acts directly on mitochondria. In the present study, oxidative stress was induced in the human RPE cell line (ARPE-19) using 4-hydroxynonenal (4-HNE) or C2-ceramide. The protective effect of Trx2 against oxidative stress was investigated by assessing cell viability, the kinetics of cell death, mitochondrial metabolic activity, and expression of heat shock proteins (Hsps) in Trx2-overexpressing cell lines generated by transfecting ARPE cells with an adeno-associated virus vector encoding Trx2. We show that overexpression of Trx2 reduced cell death induced by both agents when they were present in low concentrations. Moreover, early after the induction of oxidative stress Trx2 played a key role in the maintenance of the cell viability through upregulation of mitochondrial metabolic activity and inhibition of Hsp70 expression.

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Biochem Biophys Res Commun. 2013 Dec 6. pii: S0006-291X(13)02025-1. doi: 10.1016/j.bbrc.2013.11.113. [Epub ahead of print]

Alpha-melanocyte stimulating hormone protects retinal pigment epithelium cells from oxidative stress through activation of melanocortin 1 receptor-Akt-mTOR signaling.

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Abstract: Patients with age related macular degeneration (AMD) will develop vision loss in the center of the visual field. Reactive oxygen species (ROS)-mediated retinal pigment epithelium (RPE) cell apoptosis is an important contributor of AMD. In this study, we explored the pro-survival effect of α-melanocyte stimulating hormone (α-MSH) on oxidative stressed RPE cells. We found that α-MSH receptor melanocortin 1 receptor (MC1R) was functionally expressed in primary and transformed RPE cells. RPE cells were response to α-MSH stimulation. α-MSH activated Akt/mammalian target of rapamycin (mTOR) and Erk1/2 signalings in RPE cells, which were inhibited by MC1R siRNA knockdown. α-MSH protected RPE cells from hydrogen peroxide (H2O2)-induced apoptosis, an effect that was almost abolished when MC1R was depleted by siRNA. α-MSH-mediated S6K1 activation and pro-survival effect against H2O2 was inhibited by Akt inhibitors (perifosine, MK-2206 and LY294002). Further, mTOR inhibition by rapamycin, or by mTOR siRNA knockdown, diminished α-MSH's pro-survival effect in RPE cells. Thus, Akt and its downstream mTOR signaling mediates α-MSH-induced survival in RPE cells. In summary, we have identified a new α-MSH-MC1R physiologic pathway that reduces H2O2-induced RPE cell damage, and might minimize the risk of developing AMD.

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Diet & lifestyle

Planta Med. 2013 Dec 9. [Epub ahead of print]

Curcumin: Therapeutical Potential in Ophthalmology.

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Abstract: Curcumin (diferuloylmethane) is the main curcuminoid of the popular Indian spice turmeric (Curcuma longa). In the last 50 years, in vitro and in vivo experiments supported the main role of polyphenols and curcumin for the prevention and treatment of many different inflammatory diseases and tumors.The anti-inflammatory, antioxidant, and antitumor properties of curcumin are due to different cellular mechanisms: this compound, in fact, produces different responses in different cell types. Unfortunately, because of its low solubility and oral bioavailability, the biomedical potential of curcumin is not easy to exploit; for this reason more attention has been given to nanoparticles and liposomes, which are able to improve curcumin's bioavailability. Pharmacologically, curcumin does not show any dose-limiting toxicity when it is administered at doses of up to 8 g/day for three months. It has been demonstrated that curcumin has beneficial effects on several ocular diseases, such as chronic anterior uveitis, diabetic retinopathy, glaucoma, age-related macular degeneration, and dry eye syndrome. The purpose of this review is to report what has so far been elucidated about curcumin properties and its potential use in ophthalmology.

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Klin Monbl Augenheilkd. 2013 Dec;230(12):1251-6. doi: 10.1055/s-0033-1351029. Epub 2013 Dec 10.

[Coping with wet age-related macular degeneration - a study from Switzerland].[Article in German]

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Background: Age-related macular degeneration (AMD) affects the quality of life of about 40,000 patients in Switzerland. The treatment of wet AMD with intravitreal injected anti-vascular endothelial growth factor (VEGF) can be a heavy burden for many patients. The aim of this study was to understand the quality of life of the patients and to seek ways to improve the treatment compliance.

Methods: Half-structured telephone interviews with 28 patients between 56 and 94 years of age were transcribed and analysed. In 21 patients, both eyes were concerned with AMD.

Results: The quality of life of patients with AMD is reduced. Many activities of daily living are hindered. Dependence on others increases. Communication of the diagnosis is perceived as a shock. Most interviewees wish for more information about their specific situation. Auxiliary means and counselling possibilities are hardly known.

Conclusion: Wet AMD impacts on the quality of life of the patient. Treatment should therefore not be limited to the medical treatment of the ill eye. Triage to rehabilitation and counselling services should be included as important duties of the medical practitioners.

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Resveratrol inhibits proliferation of hypoxic choroidal vascular endothelial cells.

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PURPOSE: Resveratrol, a polyphenolic phytoalexin present in red wine, has a protective role against tumor -induced angiogenesis. Exudative age-related macular degeneration is characterized by hypoxia-induced

choroidal vascular endothelial cell (CVEC) proliferation. In this study, we evaluated the effect of resveratrol on hypoxic CVECs and the underlying signaling pathways involved.

METHODS: CVECs (RF/6A) after induction of hypoxia with cobalt chloride (CoCl2, 200 μM) were exposed to increasing doses of resveratrol (2, 4, 6, 8, 10, and 12 μg/ml). Cell viability was measured with 4-[3-(4Iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1, 3-benzene disulfonate (WST-1) colorimetric assay. The effect of resveratrol on hypoxia-induced vascular endothelial growth factor (VEGF) release was analyzed with enzyme-linked immunosorbent assay. The mechanistic pathway was further evaluated by analyzing phosphorylated stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) using immunoblot and cleaved caspase-3 with In-Cell enzyme-linked immunosorbent assay.

RESULTS: Resveratrol inhibited hypoxic CVEC proliferation. Hypoxia-induced VEGF release (30.9±2.6 pg/ml) was inhibited in a dose-dependent fashion by 2, 4, 6, 8, 10, and 12 μg/ml resveratrol to 12.4±2.1, 11.0±1.9, 10.3±3.0, 7.5±1.9, 5.5±2.0, and 5.5±2.3 pg/ml, respectively. SAPK/JNK increased by 1.8-fold and 3.9-fold after treatment with 4 and 12 μg/ml resveratrol, respectively. Significant increase in caspase-3 levels was observed with 12 μg/ml resveratrol.

CONCLUSIONS: Our study demonstrates that resveratrol suppresses hypoxic CVEC proliferation through activation of the SAPK/JNK pathway. Resveratrol, a nutritional supplement and inhibitor of CVECs, may be a useful adjunct to current anti-VEGF therapy in wet age-related macular degeneration.

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