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MD Research News

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Drug treatment

Ophthalmology. 2012 Apr 13. [Epub ahead of print]

Cost-Effectiveness Analysis of Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema.

Dewan V, Lambert D, Edler J, Kymes S, Apte RS.

Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, Missouri.

OBJECTIVE: Perform a cost-effectiveness analysis of the treatment of diabetic macular edema (DME) with ranibizumab plus prompt or deferred laser versus triamcinolone plus prompt laser. Data for the analysis were drawn from reports of the Diabetic Retinopathy Clinical Research Network (DRCRnet) Protocol I.

DESIGN: Computer simulation based on Protocol I data. Analyses were conducted from the payor perspective.

PARTICIPANTS: Simulated participants assigned characteristics reflecting those seen in Protocol I.

METHODS: Markov models were constructed to replicate Protocol I's 104-week outcomes using a microsimulation approach to estimation. Baseline characteristics, visual acuity (VA), treatments, and complications were based on Protocol I data. Costs were identified by literature search. One-way sensitivity analysis was performed, and the results were validated against Protocol I data.

MAIN OUTCOME MEASURES: Direct cost of care for 2 years, change in VA from baseline, and incremental cost-effectiveness ratio (ICER) measured as cost per additional letter gained from baseline (Early Treatment of Diabetic Retinopathy Study).

RESULTS: For sham plus laser (S+L), ranibizumab plus prompt laser (R+pL), ranibizumab plus deferred laser (R+dL), and triamcinolone plus laser (T+L), effectiveness through 104 weeks was predicted to be 3.46, 7.07, 8.63, and 2.40 letters correct, respectively. The ICER values in terms of dollars per VA letter were $393 (S+L vs. T+L), $5943 (R+pL vs. S+L), and $20 (R+dL vs. R+pL). For pseudophakics, the ICER value for comparison triamcinolone with laser versus ranibizumab with deferred laser was $14 690 per letter gained. No clinically relevant changes in model variables altered outcomes. Internal validation demonstrated good similarity to Protocol I treatment patterns.

CONCLUSIONS: In treatment of phakic patients with DME, ranibizumab with deferred laser provided an additional 6 letters correct compared with triamcinolone with laser at an additional cost of $19 216 over 2 years. That would indicate that if the gain in VA seen at 2 years is maintained in subsequent years, then the

treatment of phakic patients with DME using ranibizumab may meet accepted standards of cost-effectiveness. For pseudophakic patients, first-line treatment with triamcinolone seems to be the most cost-effective option.

PMID: 22503301 [PubMed - as supplied by publisher]

Eye (Lond). 2012 Apr;26 Suppl 2:S1-S16. doi: 10.1038/eye.2012.32.

Management of retinal vascular diseases: a patient-centric approach.

Brand CS.

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Abstract

Retinal vascular diseases are a leading cause of blindness in the Western world. Advancement in the clinical management of these diseases has been fast-paced, with new treatments becoming available as well as license extensions of existing treatments. Vascular endothelial growth factor (VEGF) has been implicated in certain retinal vascular diseases, including wet age-related macular degeneration (AMD), diabetic macular oedema (DMO), and retinal vein occlusion (RVO). Treatment of wet AMD and visual impairment due to either DMO or macular oedema secondary to RVO with an anti-VEGF on an as needed basis, rather than a fixed schedule, allows an individualised treatment approach; providing treatment when patients are most likely to benefit from it, while minimising the number of unnecessary intravitreal injections. Thus, an individualised treatment regimen reduces the chances of over-treatment and under-treatment, optimising both the risk/benefit profile of the treatment and the efficient use of NHS resource. Streamlining of treatment for patients with wet AMD and visual impairment due to either DMO or macular oedema secondary to RVO, by using one treatment with similar posology across all three diseases, may help to minimise burden of clinic capacity and complexity and hence optimise patient outcomes. Informed treatment decisions and efficient clinic throughput are important for optimal patient outcomes in the fast-changing field of retinal vascular diseases.

PMID: 22495396 [PubMed - in process] PMCID: PMC3290455

Curr Diabetes Rev. 2012 Apr 20. [Epub ahead of print]

Anti-vascular endothelial growth factor drug treatment of diabetic macular edema: the evolution continues.

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Abstract

Diabetes mellitus is the leading cause of blindness in working aged patients in developing nations. Due to the buildup of abnormal metabolites from several overactive biochemical pathways, chronic hyperglycemia causes oxidative stress in the retina which upregulates vascular endothelial growth factor (VEGF). Together with other growth factors and metabolites, VEGF causes endothelial cell proliferation, vasodilation, recruitment of inflammatory cells, and increased vascular permeability, leading to breakdown of the blood-retinal barrier. This allows trans-cellular exudation into the interstitial space resulting in diabetic macular edema (DME). For over 3 decades the standard treatment for DME has been laser photocoagulation. Though laser reduces the incidence of vision loss by 50%, few eyes with diffuse edema experience improved vision. This has led physicians to use the VEGF-binding drugs pegaptanib, ranibizumab, and

aflibercept, each of which has been approved for the treatment of exudative macular degeneration, and bevacizumab which is commonly used off-label for a variety of chorioretinal disorders. Intravitreal administration of each drug frequently causes rapid improvement of DME with sustained improvement in vision through 2 years. Though these drugs significantly outperform laser photocoagulation over treatment periods of 1 year of less, the advantages appear to lessen when trials approach 2 years. Further studies to better determine relative efficacies of anti-VEGF drugs and laser photocoagulation are continuing.

PMID: 22515701 [PubMed - as supplied by publisher]

Curr Eye Res. 2012 May;37(5):438-45.

Evaluation of Changes in Choroidal Neovascularization Secondary to Age-related Macular Degeneration after Anti-VEGF Therapy Using Spectral Domain Optical Coherence Tomography.

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Department of Ophthalmology, Konkuk University Medical Center, Konkuk University School of Medicine , Seoul , Republic of Korea.

Purpose: To evaluate the changes in choroidal neovascularization (CNV) after anti-VEGF therapy for treatment of age-related macular degeneration (AMD) using spectral domain optical coherence tomography (SD OCT).

Materials and Methods: This retrospective study included 65 eyes of 65 patients with CNV secondary to AMD. All patients underwent SD OCT before and 4 weeks after three intravitreal injections of bevacizumab (bevacizumab group) or ranibizumab (ranibizumab group). The diameter and thickness of CNV were measured from SD OCT images.

Results: Retinal edema was completely resolved in 57%, partially resolved in 28% and unchanged in 15% of all post-injection SD OCTs. The resolution rate of retinal edema was not significantly different between the bevacizumab and ranibizumab group ($p = 0.960$). In all CNV types, the diameter of CNV did not show significant change after treatment; the average diameter changed from 2923 to 2888 μm in classic CNV and from 2378 to 2338 μm in occult CNV in bevacizumab group; from 2691 to 2580 μm in classic CNV and from 2731 to 2337 μm in occult CNV in ranibizumab group. However, the thickness of CNV showed a significant reduction in classic CNV of both the bevacizumab group (from 301 to 233 μm, $p = 0.012$, reduction rate 22%) and the ranibizumab group (from 258 to 213 μm, $p = 0.025$, reduction rate 17%). In occult CNV, the thickness of CNV showed a significant reduction only in the ranibizumab group (from 163 to 146 μm, $p = 0.033$, reduction rate 10%).

Conclusions: Anti-VEGF therapy for the treatment of AMD may reduce the thickness of CNV and thus result in morphologic stability of CNV. Although morphologic regression of CNV is not achieved, further CNV growth could be arrested with anti-VEGF therapy.

PMID: 22510011 [PubMed - in process]

Curr Eye Res. 2012 May;37(5):399-407.

Retinal function and morphology in rabbit after intravitreal injection of VEGF inhibitors.

Myers AC, Lövestam Adrian M, Bruun A, Ghosh F, Andréasson S, Ponjavic V.

Department of Ophthalmology, Lund University , Lund , Sweden.

Purpose/Aim: To explore changes in morphology and function in the rabbit retina after intravitreal high-dose injection of three commonly used VEGF inhibitors.

Materials and methods: Forty-eight rabbits of mixed strain (6 months of age, body weight ≈ 3 kg) were randomized into four groups (n = 12). They were examined with full-field electroretinography (ERG) and with multifocal electroretinography (mf ERG) prior to drug exposure. The rabbits were then injected intravitreally with bevacizumab, ranibizumab, pegaptanib, or with a balanced saline solution. The dose of VEGF inhibitor was chosen to achieve a vitreous concentration approximately three times higher than the one clinically used in the adult human eye. ERG was then performed 8 weeks postinjection, and mf ERG 9 weeks postinjection. After 9 weeks, the rabbits were sacrificed and the sectioned retina was studied. Immunohistochemical analysis was performed of rods, cones, rod bipolar cells, horizontal cells, and amacrine cells.

Results: Rabbits injected with VEGF inhibitors all showed significantly lower amplitude of the dark-adapted b-wave rod-mediated response to dim light, compared to the rabbits injected with BSS. The a wave (reflecting photoreceptor function) in the response to single flash white light was however not affected. Immunohistochemistry revealed a significant reduction in PKC labeling of rod bipolar cells in pegaptanib and ranibizumab injected eyes whereas bevacizumab injected eyes displayed normal PKC labeling. No apparent morphological change was seen with markers for remaining retinal cells.

Conclusions: Our results indicate that the use of high-dose intravitreal VEGF inhibitors in the rabbit eye affects rod-mediated retinal function and PKC expression in rod bipolars cells for at least 9 weeks after drug administration. The three VEGF inhibitors influence the retina slightly differently. These results are important for the understanding of drug action and when devising therapeutical strategies in new areas such as retinopathy of prematurity where vitreous volume is significantly lower compared to the adult eye.

PMID: 22510009 [PubMed - in process]

Am J Ophthalmol. 2012 May;153(5):1004-5.

Combined intravitreal ranibizumab and photodynamic therapy for retinal angiomatous proliferation.

Lee MY, Kim KS, Lee WK.

Seoul, Korea.

PMID: 22516155 [PubMed - in process]

Other treatment & diagnosis

J Tissue Eng Regen Med. 2012 Apr 18. doi: 10.1002/term.1458. [Epub ahead of print]

Differentiation of human pluripotent stem cells to retinal pigmented epithelium in defined conditions using purified extracellular matrix proteins.

Rowland TJ, Blaschke AJ, Buchholz DE, Hikita ST, Johnson LV, Clegg DO.

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Abstract

A potential application of human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) is the generation of retinal pigmented epithelium (RPE) to treat age-related macular degeneration (AMD), a common but incurable retinal disease. RPE cells derived from hESCs (hESC-RPEs) and iPSCs (iPSC-RPEs) express essential RPE markers and can rescue visual function in animal models. However, standard differentiation protocols yield RPE cells at low frequency, especially from iPSC lines, and the common use

of Matrigel and xenogeneic feeder cells is not compatible with clinical applications. The extracellular matrix (ECM) can affect differentiation, and therefore changes in ECM composition may improve the frequency of stem cell-RPE differentiation. We selected several purified ECM proteins and substrates, based on the in vivo RPE ECM environment, and tested their ability to support iPSC-RPE differentiation and maintenance. iPSCs differentiated on nearly all tested substrates developed pigmented regions, with Matrigel and mouse laminin-111 supporting the highest pigmentation frequencies. Although iPSC-RPEs cultured on the majority of the tested substrates expressed key RPE genes, only six substrates supported development of confluent monolayers with normal RPE morphology, including Matrigel and mouse laminin-111. iPSCs differentiated on mouse laminin-111 produced iPSC-RPEs expressing RPE proteins, and hESCs differentiated on mouse laminin-111 resulted in high yields of functional hESC-RPEs. This identification of key ECM proteins may assist with future scaffold designs and provide peptide sequences for use in synthetic, xeno-free, GMP-compliant generation of RPE from human pluripotent stem cells relevant to clinical translation.

PMID: 22514096 [PubMed - as supplied by publisher]

Ophthalmology. 2012 Apr 17. [Epub ahead of print]

Fundus Autofluorescence in Polypoidal Choroidal Vasculopathy.

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Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

PURPOSE: To investigate and compare the characteristics of fundus autofluorescence (FAF) in polypoidal choroidal vasculopathy (PCV) with those in typical neovascular age-related macular degeneration (AMD).

DESIGN: Retrospective, observational, consecutive case series.

PARTICIPANTS: Ninety-two patients with PCV (92 affected eyes and 86 unaffected fellow eyes) and 31 patients with typical neovascular occult AMD with no classic choroidal neovascularization (31 affected eyes and 24 unaffected fellow eyes).

METHODS: All study eyes underwent FAF photography with a fundus camera-based system. The incidence and distribution of hypoautofluorescence, that is, the manifestation of retinal pigment epithelium (RPE) damages, were evaluated.

MAIN OUTCOME MEASURES: The characteristic FAF findings in PCV.

RESULTS: In the affected eyes with PCV, the sites of the neovascular lesions showed 2 distinct FAF patterns: (1) the confluent hypoautofluorescence at the polypoidal lesions and (2) the granular hypoautofluorescence at the branching choroidal vascular networks. The confluent hypoautofluorescence, most of which was surrounded by a hyperautofluorescent ring, was seen in 74 eyes (80.4%) with PCV but was seen in no eyes with typical neovascular AMD ($P < 0.001$). The granular hypoautofluorescence was seen in 91 eyes (98.9%) with PCV and 27 eyes (87.1%) with typical neovascular AMD ($P = 0.014$). In addition, the eyes with PCV more frequently showed hypoautofluorescence outside the macular area than those with typical neovascular AMD ($P = 0.021$). In the unaffected fellow eyes, the hypoautofluorescence was more frequently observed in patients with PCV than in those with typical neovascular AMD, inside the macular area and in the entire FAF image ($P = 0.012$, $P = 0.003$, respectively).

CONCLUSIONS: In eyes with PCV, the polypoidal lesions and the branching choroidal vascular networks appeared to affect the RPE and induce peculiar FAF findings. When compared with the patients with typical neovascular AMD, widespread RPE damage was more frequently observed in the patients with PCV, both in the affected eyes and in the unaffected fellow eyes.

PMID: 22512987 [PubMed - as supplied by publisher]

Ophthalmology. 2012 Apr 17. [Epub ahead of print]

Photographic Assessment of Baseline Fundus Morphologic Features in the Comparison of Age-Related Macular Degeneration Treatments Trials.

Grunwald JE, Daniel E, Ying GS, Pistilli M, Maguire MG, Alexander J, Whittock-Martin R, Parker CR, Sepielli K, Blodi BA, Martin DF; CATT Research Group.

Scheie Eye Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; Center for Preventive Ophthalmology and Biostatistics, Department of Ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

OBJECTIVE: To describe the methods used for assessment of baseline fundus characteristics from color photography and fluorescein angiography (FA) in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and to describe the relationship between these characteristics and visual acuity.

DESIGN: Randomized, masked, multicenter trial.

PARTICIPANTS: This investigation included 1185 participants of the CATT study.

METHODS: Baseline stereoscopic color fundus photographs and FAs of participants in the CATT study were assessed at a central fundus photograph reading center by masked readers. Replicate assessments of random samples of photographs were performed to assess intragrader and intergrader agreements. The association of the lesion characteristics with baseline visual acuity was assessed using analyses of variance and correlation coefficients.

MAIN OUTCOME MEASURES: Intragrader and intergrader reproducibility, visual acuity, and lesion characteristics.

RESULTS: Intragrader and intergrader reproducibility showed agreements ranging from 75% to 100% and weighted κ values ranging from 0.48 to 1.0 for qualitative determinations. The intraclass correlation coefficients were 0.96 to 0.97 for quantitative measurements of choroidal neovascularization (CNV) area and total area of CNV lesion. The mean visual acuity varied by the type of pathologic features in the foveal center: 64.5 letters (standard error, 0.7 letters) for fluid only, 59.0 letters (standard error, 0.5 letters) for CNV, and 58.7 letters (standard error, 1.3 letters) for hemorrhage ($P<0.001$). Fibrotic or atrophic scar present in the lesion, but not under the center of the fovea, also was associated with a markedly reduced visual acuity of 48.4 letters (standard error, 2.2 letters; $P<0.0001$). Although total area of CNV lesion was correlated weakly with visual acuity when all participants were assessed (Spearman correlation coefficient, $\rho = -0.16$; $P<0.001$), the correlation was stronger within patients with predominantly classic lesions ($\rho = -0.42$; $P<0.001$).

CONCLUSIONS: These results show that the methodology used for grading CATT fundus images has good reproducibility. As expected, larger total CNV lesion area and pathologic findings such as hemorrhage, fibrosis, and atrophy at baseline are associated with decreased visual acuity.

PMID: 22512984 [PubMed - as supplied by publisher]

Med Educ. 2012 May;46(5):517-8. doi: 10.1111/j.1365-2923.2012.04238.x.

E-learning strategies to improve general practitioners' knowledge of age-related macular degeneration.

Coco RM, Sanabria MR, Fernandez I.

PMID: 22515775 [PubMed - in process]

Pathogenesis

Mol Aspects Med. 2012 Apr 9. [Epub ahead of print]

Consequences of oxidative stress in age-related macular degeneration.

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Abstract

The retina resides in an environment that is primed for the generation of reactive oxygen species (ROS) and resultant oxidative damage. The retina is one of the highest oxygen-consuming tissues in the human body. The highest oxygen levels are found in the choroid, but this falls dramatically across the outermost retina, creating a large gradient of oxygen towards the retina and inner segments of the photoreceptors which contain high levels of polyunsaturated fatty acids. This micro-environment together with abundant photosensitizers, visible light exposure and a high energy demand supports a highly oxidative milieu. However, oxidative damage is normally minimized by the presence of a range of antioxidant and efficient repair systems. Unfortunately, as we age oxidative damage increases, antioxidant capacity decreases and the efficiency of reparative systems become impaired. The result is retinal dysfunction and cell loss leading to visual impairment. It appears that these age-related oxidative changes are a hallmark of early age-related macular degeneration (AMD) which, in combination with hereditary susceptibility and other retinal modifiers, can progress to the pathology and visual morbidity associated with advanced AMD. This review reassesses the consequences of oxidative stress in AMD and strategies for preventing or reversing oxidative damage in retinal tissues.

PMID: 22510306 [PubMed - as supplied by publisher]

Mol Aspects Med. 2012 Apr 5. [Epub ahead of print]

How does the macula protect itself from oxidative stress?

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Abstract

Oxidative stress has been hypothesized to contribute to the development of age-related macular degeneration (AMD), the most common cause of blindness in the United States. At present, there is no treatment for early disease. Reactive oxygen species (ROS) play a physiological role in the retinal pigment epithelium (RPE), a key cell type in this disease, but with excessive ROS, oxidative damage or excessive innate immune system activation can result. The RPE has developed a robust antioxidant system driven by the transcription factor Nrf2. Impaired Nrf2 signaling can lead to oxidative damage or activate the innate immune response, both of which can lead to RPE apoptosis, a defining change in AMD. Several mouse models simulating environmental stressors or targeting specific antioxidant enzymes such as superoxide dismutase or Nrf2, have simulated some of the features of AMD. While ROS are short-lived, oxidatively damaged molecules termed oxidation specific epitopes (OSEs), can be long-lived and a source of chronic stress that activates the innate immune system through pattern recognition receptors (PRRs). The macula accumulates a number of OSEs including carboxyethylpyrrole, malondialdehyde, 4-hydroxynonenal, and advanced glycation endproducts, as well as their respective neutralizing PRRs. Excessive accumulation of OSEs results in pathologic immune activation. For example, mice immunized with the carboxyethylpyrrole develop cardinal features of AMD. Regulating ROS in the RPE by modulating antioxidant systems or

neutralizing OSEs through an appropriate innate immune response are potential modalities to treat or prevent early AMD.

PMID: 22503691 [PubMed - as supplied by publisher]

Curr Neurovasc Res. 2011 Apr 19. [Epub ahead of print]

The Many Facets of Cell Injury: Angiogenesis to Autophagy.

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Abstract

Throughout the body, injury to cells and subsequent loss of tissue or organ can be the result from multiple etiologies. Under some conditions, cells that normally provide vital support for the development and maturation of tissues may sometimes also lead to the detriment of other cells and systems in the body. One example of this pertains to vascular cells and the process of angiogenesis. Angiogenesis is the process of fostering new capillary formation from pre-existing vessels into an avascular area. Angiogenesis is present during development such as during embryogenesis, during menstruation, and also during reparative processes for wound healing. During periods of acute injury such as a stroke, cytokines and growth factors can promote proteins for angiogenesis such as Tie-2 and angiopoietin-2. With new vessel formation, cerebral blood flow to previously ischemic areas of the brain can be restored. Angiogenesis also has a significant role during organ transplantation since new vessel formation can be crucial to successfully prevent allograft rejection. New vessel formation also may be vital for stem cell transplantation, cell migration, and cellular differentiation for regeneration of the host tissue. Yet, angiogenesis that is without limits can be detrimental and foster tumorigenesis and metastatic disease. In other scenarios, excessive vascular growth with angiogenesis can lead to ocular neovascularization, a principal cause of blindness during diseases such as age-related macular degeneration and diabetic neuropathy. In addition to the role of the vascular system during pathological disease processes, cells that incur primary injury also can impact the ability to recover from an acute or chronic insult. Primary injury to cells can occur during apoptosis or autophagy. Apoptosis represents a spectrum of early and late processes. The early energy dependent phase that involves the externalization of phosphatidylserine residues on the surface of cells can be a signal for inflammatory cells, such as microglia, to engulf and dispose of injured cells that have phosphatidylserine residue exposure. This process may assist with the repair and regeneration of injured tissues to remove non-functional dying cells, but also at times may lead to the removal of otherwise functional cells if not kept in-check. The late phase of apoptosis usually does not allow for the repair or recovery of cells since it involves nuclear DNA degradation. In contrast to the process of apoptosis is autophagy. Autophagy allows cells to recycle cytoplasmic components, dispose of defective organelles, but preserve necessary cytoskeletal structures during development, cell differentiation, and tissue remodeling. However, autophagy also can lead to cell death especially during acute injury and be a contributing factor to several disorders. For example, during experimental focal or global cerebral ischemia, prevention of autophagy can limit cerebral infarct size and protect hippocampal neurons. In this issue of Current Neurovascular Research, a series of original papers illustrate the intricate role that vascular cell proliferation, vascular dysfunction, and intrinsic cell pathways that lead to apoptosis and autophagy may contribute to disease pathology. Ciancarelli and co-authors show in small population of patients following ischemic stroke onset that these patients suffer from redox in balance through elevated oxidative stress parameters that may be attributed to endothelial cell activation and dysfunction. At the cellular neuronal level during oxidant stress, Wang and colleagues illustrate that targeting the Wnt1 inducible signaling pathway protein 1 (WISP1/CCN4) and its control over the □-catenin pathway may offer a unique strategy against apoptotic neurodegeneration. Interestingly, the study suggests that in their model of acute neurodegeneration, autophagy appears to involve only a small population of neurons without significant

impact upon overall neuronal cell survival. Our next study by Umigat et al. brings us into the realm of vascular proliferation and the potential for disease progression. These authors show that a carotenoid derivative, crocetin, an agent previously demonstrated to block retinal damage can effectively suppress vascular endothelial growth factor mediated angiogenesis, suggesting a future role for crocetin and agents with similar mechanisms for treatment against disorders such as age-related macular degeneration and diabetic neuropathy. Sarkar et al. further highlight the role of vascular endothelial cell activation during acute brain injury with their demonstration that up-regulation of laminin expression may affect the proliferation and migration of reactive astrocytes during cerebral injury, suggesting that vascular endothelial activation could become the initial target for the treatment of acute brain lesions. In patients with multiple sclerosis, Ciccone and authors suggest that monitoring chronic cerebrospinal venous insufficiency may be an important strategy for following the onset and progression of multiple sclerosis, since chronic cerebrospinal venous insufficiency and vascular dysfunction may be an important contributing factor in this immune mediated disease. In another clinical study, Luo et al. illustrate that patients with acute ischemic stroke had elevated levels of serum bilirubins that may be a potential biomarker for stroke severity and the generation of oxidative stress that would affect multiple systems including the vascular, neuronal, and immune systems. Given the significant impact angiogenesis can play in cell death as well as tumor progression, Chen and colleagues describe the development of a novel treatment using nanoparticles encoding vasohibin and RGD 12-mer cationic peptide RKKRRQRRRRGD that can prevent tumor angiogenesis and inhibit tumor growth by attenuating neovasculature formation and inducing tumor apoptosis. In our final paper for this issue, Cook et al. offer a new treatment using sustained-release formulations of dihydropyridines against vascular dysfunction and vasospasm that occurs during the devastating condition of subarachnoid hemorrhage that can lead to cerebral infarction. The original studies in this this issue of Current Neurovascular Research offer our readers an exciting spectrum of work for effective drug development that identifies cellular mediators of disease pathology, in this case excessive vascular proliferation, vascular dysfunction, and apoptotic/autophagic intrinsic cellular pathways, as well as thought-provoking clinical studies that can foster the development of novel treatment strategies for disorders ranging from neurodegeneration to tumorigenesis.

PMID: 22515176 [PubMed - as supplied by publisher]

Arterioscler Thromb Vasc Biol. 2012 Apr 19. [Epub ahead of print]

Intense Physiological Light Upregulates Vascular Endothelial Growth Factor and Enhances Choroidal Neovascularization via Peroxisome Proliferator-Activated Receptor γ Coactivator-1α in Mice.

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OBJECTIVE: Toxicity of intense light to facilitate the development of neovascular age-related macular degeneration has been a health concern although the mechanism remains unclear.

METHODS AND RESULTS: Effects of intense, but within physiological range, light on retinal pigment epithelium, a major pathogenic origin of age-related macular degeneration were studied in mice. Intense physiological light upregulated vascular endothelial growth factor (VEGF) expression in retinal pigment epithelium, independent of circadian rhythm, which resulted in enhancement of choroidal neovascularization. In rd1/rd1 mice or Crx(-/-) mice that do not possess outer segment structure, light exposure did not induce VEGF, indicating that VEGF upregulation by light depended on increased outer segment phagocytosis by retinal pigment epithelium. In retinal pigment epithelium cells phagocytosing increased amount of outer segment, peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) not hypoxia-inducible factor-1α was induced, leading to VEGF upregulation. The VEGF upregulation and choroidal neovascularization enhancement were abrogated in PGC-1α(-/-) mice and estrogen-related receptor-α(-/-) mice, indicating the involvement of PGC-1α/estrogen-related receptor-α pathway.

CONCLUSIONS: Intense physiological light is involved in choroidal neovascularization through excess outer segment phagocytosis and VEGF upregulation mediated by PGC-1α in vivo.

PMID: 22516064 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmologica. 2012 Apr 13. [Epub ahead of print]

Two-Year Course of Subfoveal Pigment Epithelial Detachment in Eyes with Age-Related Macular Degeneration and Visual Acuity Better than 20/40.

Baba T, Kitahashi M, Kubota-Taniai M, Oshitari T, Yamamoto S.

Department of Ophthalmology and Visual Science, Chiba University Graduate School of Medicine, Chiba, Japan.

Purpose: To investigate the course of subfoveal pigment epithelial detachments (PEDs) in eyes with age-related macular degeneration (AMD) and best-corrected visual acuity (BCVA) ≥20/40.

Methods: Thirty-seven eyes of 35 patients with a subfoveal PED were divided into an avascular PED group (n = 11), a vascularized PED group due to polypoidal choroidal vasculopathy (PCV, n = 14) and an occult choroidal neovascularization (CNV) group (n = 12). Intravitreal bevacizumab or ranibizumab was given as needed. The BCVA, central foveal thickness, PED thickness, and lesion size were measured at baseline and at 2 years after the initial examination.

Results: The BCVA did not change significantly in the avascular group, decreased from 0.06 ± 0.11 to 0.23 ± 0.15 logMAR units in the PCV group and from 0.12 ± 0.12 to 0.71 ± 0.70 logMAR units in the CNV group. At 2 years, the central foveal and PED thicknesses were not significantly different among the 3 groups, and the lesion was significantly larger in the PCV and CNV groups than in the avascular group.

Conclusions: The vascularized PED cases had a poorer visual outcome than avascular PEDs with anti-VEGF drugs at the 2-year follow-up.

PMID: 22508168 [PubMed - as supplied by publisher]

Genetics

Mol Aspects Med. 2012 Apr 5. [Epub ahead of print]

Complement dysregulation in AMD: RPE-Bruch's membrane-choroid.

Sparrow JR, Ueda K, Zhou J.

Abstract

The question as to why the macula of the retina is prone to an aging disease (age-related macular degeneration) remains unanswered. This unmet challenge has implications since AMD accounts for approximately 54% of blindness in the USA (Swaroop, Chew, Bowes Rickman and Abecasis, 2009). While AMD has onset in the elder years, it likely develops over time. Genetic discovery to date has accounted for approximately 50% of the inheritable component of AMD. The polymorphism that has been most widely studied is the Y402H allele in the complement factor H gene. The implication of this genetic association is that in a subset of AMD cases, unregulated complement activation is permissive for AMD. Given that this gene variant results in an amino acid substitution, it is assumed that this change will have functional consequences although the precise mechanisms are still unknown. Genetic predisposition is not the only factor however, since in this complex disease there is substantial evidence that lifestyle factors such as diet

and smoking contribute to risk. Here we provide an overview of current knowledge with respect to factors involved in AMD pathogenesis. Interwoven with these issues is a discussion of the significant role played by aging processes, some of which are unique to the retina and retinal pigment epithelium. One recurring theme is the potential for disease promotion by diverse types of oxidation products.

PMID: 22504022 [PubMed - as supplied by publisher]

Int J Biochem Mol Biol. 2012;3(1):105-16. Epub 2012 Mar 20.

Common micro RNAs (miRNAs) target complement factor H (CFH) regulation in Alzheimer's disease (AD) and in age-related macular degeneration (AMD).

Lukiw WJ, Surjyadipta B, Dua P, Alexandrov PN.

Abstract

Alzheimer's disease (AD) and age-related macular degeneration (AMD) are complex and progressive inflammatory degenerations of the human neocortex and retina. Recent molecular, genetic and epigenetic evidence indicate that at least 4 micro RNAs (miRNAs) - including the NF-κB-regulated miRNA-9, miRNA-125b, miRNA-146a and miRNA-155 - are progressively up-regulated in both AD and AMD. This quartet of up-regulated miRNAs in turn down-regulate a small brain- and retinal-cell-relevant family of target mRNAs, including that encoding complement factor H (CFH), a major negative regulator of the innate immune and inflammatory response. Together miRNA-146a and miRNA-155 recognize an overlapping miRNA regulatory control (MiRC) region in the CFH 3'-untranslated region (3'- UTR; 5'-TTTAGTATTAA-3') to which either of these miRNAs may interact. Progressive, pathogenic increases in specific miRNA binding to the entire 232 nucleotide CFH 3'-UTR appears to be a major regulator of CFH expression down-regulation, and the inflammatory pathology that characterizes both AMD and AD. The data presented in this report provides evidence that up-regulation of brain- and retinal- abundant miRNAs, including miRNA-9, miRNA-125b, miRNA-146a and miRNA-155, are common to the pathogenetic mechanism of CFH deficiency that drives inflammatory neurodegeneration, and for the first time indicates multiple, independent miRNA-mediated regulation of the CFH mRNA 3'-UTR.

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The 5HT(1a) Receptor Agonist 8-Oh DPAT Induces Protection from Lipofuscin Accumulation and Oxidative Stress in the Retinal Pigment Epithelium.

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Abstract

Age-related macular degeneration (AMD), a major cause of blindness in the elderly, is associated with oxidative stress, lipofuscin accumulation and retinal degeneration. The aim of this study was to determine if a 5-HT(1A) receptor agonist can reduce lipofuscin accumulation, reduce oxidative damage and prevent retinal cell loss both in vitro and in vivo. Autophagy-derived and photoreceptor outer segment (POS)-derived lipofuscin formation was assessed using FACS analysis and confocal microscopy in cultured retinal pigment epithelial (RPE) cells in the presence or absence of the 5-HT(1A) receptor agonist, 8-OH DPAT. 8-OH DPAT treatment resulted in a dose-dependent reduction in both autophagy- and POS-derived lipofuscin compared to control. Reduction in autophagy-induced lipofuscin was sustained for 4 weeks following removal of the drug. The ability of 8-OH DPAT to reduce oxidative damage following exposure to 200 µM H(2)O(2) was assessed. 8-OH DPAT reduced superoxide generation and increased mitochondrial superoxide dismutase (MnSOD) levels and the ratio of reduced glutathione to the oxidized form of

glutathione in H(2)O(2)-treated cells compared to controls and protected against H(2)O(2)-initiated lipid peroxidation, nitrotyrosine levels and mitochondrial damage. SOD2 knockdown mice, which have an AMD-like phenotype, received daily subcutaneous injections of either saline, 0.5 or 5.0 mg/kg 8-OH DPAT and were evaluated at monthly intervals. Systemic administration of 8-OH DPAT improved the electroretinogram response in SOD2 knockdown eyes of mice compared to knockdown eyes receiving vehicle control. There was a significant increase in the ONL thickness in mice treated with 8-OH DPAT at 4 months past the time of MnSOD knockdown compared to untreated controls together with a 60% reduction in RPE lipofuscin. The data indicate that 5-HT(1A) agonists can reduce lipofuscin accumulation and protect the retina from oxidative damage and mitochondrial dysfunction. 5-HT(1A) receptor agonists may have potential as therapeutic agents in the treatment of retinal degenerative disease.

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Mol Vis. 2012;18:816-29. Epub 2012 Apr 4.

Genetic associations in polypoidal choroidal vasculopathy: A systematic review and meta-analysis.

Chen H, Liu K, Chen LJ, Hou P, Chen W, Pang CP.

PURPOSE: To investigate the genetic associations of polypoidal choroidal vasculopathy (PCV), the genetic difference between PCV and age-related macular degeneration (AMD), and the genotype-phenotype correlation of PCV.

METHODS: A systematic review and meta-analysis were performed. Published articles about genetic associations of PCV identified from a literature search were reviewed. The following data from individual studies were extracted and analyzed: 1) comparison of genetic polymorphisms between PCV and controls; 2) comparison of genetic polymorphisms between PCV and AMD; and 3) comparison of phenotypes between different genotype groups.

RESULTS: A total of 33 articles fulfilled the inclusion criteria. With meta-analyses, variants in four genes were found to be significantly associated with PCV: LOC387715 rs10490924 (n=9, allelic odds ratio [OR] =2.27, p<0.00001), HTRA1 rs11200638 (n=4, OR=2.72, p<0.00001), CFH rs1061170 (n=4, OR=1.72, p<0.00001), CFH rs800292 (n=5, OR=2.10, p<0.00001), and C2 rs547154 (n=3, OR=0.56, p=0.01). LOC387715 rs10490924 was the only variant showing a significant difference between PCV and wet AMD (n=5, OR=0.66, p<0.00001). The risk genotypes of rs10490924 were associated with larger lesion size, greater chance of vitreous hemorrhage, and worse therapeutic response in PCV.

CONCLUSIONS: LOC387715 rs10490924 was associated with PCV and its clinical manifestations, and showed a discrepant distribution between PCV and AMD. Variants in HTRA1, CFH, and C2 were also associated with PCV.

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Multicenter cohort association study of SLC2A1 single nucleotide polymorphisms and age-related macular degeneration.

Baas DC, Ho L, Tanck MW, Fritsche LG, Merriam JE, van Het Slot R, Koeleman BP, Gorgels TG, van Duijn CM, Uitterlinden AG, de Jong PT, Hofman A, Ten Brink JB, Vingerling JR, Klaver CC, Dean M, Weber BH, Allikmets R, Hageman GS, Bergen AA.

PURPOSE: Age-related macular degeneration (AMD) is a major cause of blindness in older adults and has a genetically complex background. This study examines the potential association between single nucleotide polymorphisms (SNPs) in the glucose transporter 1 (SLC2A1) gene and AMD. SLC2A1 regulates the bioavailability of glucose in the retinal pigment epithelium (RPE), which might influence oxidative stress-mediated AMD pathology.

METHODS: Twenty-two SNPs spanning the SLC2A1 gene were genotyped in 375 cases and 199 controls from an initial discovery cohort (the Amsterdam-Rotterdam-Netherlands study). Replication testing was performed in The Rotterdam Study (the Netherlands) and study populations from Würzburg (Germany), the Age Related Eye Disease Study (AREDS; United States), Columbia University (United States), and Iowa University (United States). Subsequently, a meta-analysis of SNP association was performed.

RESULTS: In the discovery cohort, significant genotypic association between three SNPs (rs3754219, rs4660687, and rs841853) and AMD was found. Replication in five large independent (Caucasian) cohorts (4,860 cases and 4,004 controls) did not yield consistent association results. The genotype frequencies for these SNPs were significantly different for the controls and/or cases among the six individual populations. Meta-analysis revealed significant heterogeneity of effect between the studies.

CONCLUSIONS: No overall association between SLC2A1 SNPs and AMD was demonstrated. Since the genotype frequencies for the three SLC2A1 SNPs were significantly different for the controls and/or cases between the six cohorts, this study corroborates previous evidence that population dependent genetic risk heterogeneity in AMD exists.

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Diet

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Nutritional modulation of age-related macular degeneration.

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Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly worldwide. It affects 30-50 million individuals and clinical hallmarks of AMD are observed in at least one third of persons over the age of 75 in industrialized countries (Gehrs et al., 2006). Costs associated with AMD are in excess of $340 billion US (American-Health-Assistance-Foundation, 2012). The majority of AMD patients in the United States are not eligible for clinical treatments (Biarnes et al., 2011; Klein et al., 2011). Preventive interventions through dietary modulation are attractive strategies because many studies suggest a benefit of micro- and macronutrients with respect to AMD, as well as other age-related debilities, and with few, if any, adverse effects (Chiu, 2011). Preservation of vision would enhance quality of life for millions of elderly people, and alleviate the personal and public health financial burden of AMD (Frick et al., 2007; Wood et al., 2011). Observational studies indicate that maintaining adequate levels of omega-3 fatty acids (i.e. with 2 servings/week of fish) or a low glycemic index diet may be particularly beneficial for early AMD and that higher levels of carotenoids may be protective, most probably, against neovascular AMD. Intervention trials are needed to better understand the full effect of these nutrients and/or combinations of nutrients on retinal health. Analyses that describe effects of a nutrient on onset and/or progress of AMD are valuable because they indicate the value of a nutrient to arrest AMD at the early stages. This comprehensive summary provides essential information about the value of nutrients with regard to diminishing risk for onset or progress of AMD and can serve as a guide until data from ongoing intervention trials are available.

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Vitamins E and C and Medical Record-Confirmed Age-Related Macular Degeneration in a Randomized Trial of Male Physicians.

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PURPOSE: To test whether supplementation with alternate-day vitamin E or daily vitamin C affects the incidence of the diagnosis of age-related macular degeneration (AMD) in a large-scale randomized trial of male physicians.

DESIGN: Randomized, double-masked, placebo-controlled trial.

PARTICIPANTS: We included 14 236 apparently healthy United States male physicians aged ≥50 years who did not report a diagnosis of AMD at baseline.

METHODS: Participants were randomly assigned to receive 400 international units (IU) of vitamin E or placebo on alternate days, and 500 mg of vitamin C or placebo daily. Participants reported new diagnoses of AMD on annual questionnaires and medical record data were collected to confirm the reports.

MAIN OUTCOME MEASURES: Incident diagnosis of AMD responsible for a reduction in best-corrected visual acuity to ≤20/30.

RESULTS: After 8 years of treatment and follow-up, a total of 193 incident cases of visually significant AMD were documented. There were 96 cases in the vitamin E group and 97 in the placebo group (hazard ratio [HR], 1.03; 95% confidence interval [CI], 0.78-1.37). For vitamin C, there were 97 cases in the active group and 96 in the placebo group (HR, 0.99; 95% CI, 0.75-1.31).

CONCLUSIONS: In a large-scale, randomized trial of United States male physicians, alternate-day use of 400 IU of vitamin E and/or daily use of 500 mg of vitamin C for 8 years had no appreciable beneficial or harmful effect on risk of incident diagnosis of AMD.

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