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MD Research News

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Drug treatment

Am J Ophthalmol. 2011 Jan 12. [Epub ahead of print]

Intravitreal Ranibizumab for Myopic Choroidal Neovascularization: Factors Predictive of Visual Outcome and Need for Retreatment.

Calvo-Gonzalez C, Reche-Frutos J, Donate J, Fernandez-Perez C, Garcia-Feijoo J.

Ophthalmology Department, Hospital Clinico San Carlos, Madrid, Spain.

PURPOSE: To identify predictive factors for visual outcome and need for retreatment after treating myopic choroidal neovascularization (CNV) with ranibizumab.

DESIGN: A prospective interventional case series.

METHODS: Sixty-seven eyes of 67 patients with myopic CNV were treated with 3 intravitreal ranibizumab injections given monthly. Best-corrected visual acuity (BCVA) and optical coherence tomography-determined central macular thickness (CMT) were recorded monthly during follow-up. Fluorescein angiography changes and the number of injections needed were also assessed.

RESULTS: Mean follow-up was 15.9 months. Mean BCVA improved by 7.8 letters after the first injection, 12.5 letters after 3 injections, and 12 letters by end follow-up. In 53 eyes (79.1%), BCVA improved; 40.3% gained more than 15 letters. No differences were detected in visual outcome between treatment-naïve and previously treated patients. Myopic CNV area and greatest linear dimension had diminished at the study end. The mean reduction in CMT was 93.6 μm. The mean number of injections given was 4.2. A total of 53.7% of eyes received only 3 injections. Through regression analysis, baseline BCVA (P = .006) and myopic CNV location (P = .026) were significantly correlated with BCVA at the end of follow-up. Myopic CNV location (P = .023) and prior treatment (P = .047) were significantly linked to the number of injections given. No major complications arose.

CONCLUSION: An initial treatment regimen of 3 monthly ranibizumab injections seems effective and safe to treat myopic CNV. Baseline BCVA and myopic CNV location emerged as predictive factors for visual outcome. A need for retreatment was associated with myopic CNV location and prior treatment.

PMID: 21236413 [PubMed - as supplied by publisher]

Pharmacoeconomics. 2011 Feb 1;29(2):107-31. doi: 10.2165/11585520-000000000-00000.

Cost effectiveness of treatments for wet age-related macular degeneration.

Mitchell P, Annemans L, White R, Gallagher M, Thomas S.

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Abstract

Age-related macular degeneration (AMD) is a leading cause of blindness in people aged ≥50 years. Wet AMD in particular has a major impact on patient quality of life and imposes substantial burdens on healthcare systems. This systematic review examined the cost-effectiveness data for current therapeutic options for wet AMD. PubMed and EMBASE databases were searched for all articles reporting original cost -effectiveness analyses of wet AMD treatments. The Centre for Reviews and Dissemination and Cochrane Library databases were searched for all wet AMD health technology assessments (HTAs). Overall, 44 publications were evaluated in full and included in this review. A broad range of cost-effectiveness analyses were identified for the most commonly used therapies for wet AMD (pegaptanib, ranibizumab and photodynamic therapy [PDT] with verteporfin). Three studies evaluated the cost effectiveness of bevacizumab in wet AMD. A small number of analyses of other treatments, such as laser photocoagulation and antioxidant vitamins, were also found. Ranibizumab was consistently shown to be cost effective for wet AMD in comparison with all the approved wet AMD therapies (four of the five studies identified showed ranibizumab was cost effective vs usual care, PDT or pegaptanib); however, there was considerable variation in the methodology for cost-effectiveness modelling between studies. Findings from the HTAs supported those from the PubMed and EMBASE searches; of the seven HTAs that included ranibizumab, six (including HTAs for Australia, Canada and the UK) concluded that ranibizumab was cost effective for the treatment of wet AMD; most compared ranibizumab with PDT and/or pegaptanib. By contrast, HTAs at best generally recommended pegaptanib or PDT for restricted use in subsets of patients with wet AMD. In the literature analyses, pegaptanib was found to be cost effective versus usual/best supportive care (including PDT) or no treatment in one of five studies; the other four studies found pegaptanib was of borderline cost effectiveness depending on the stage of disease and time horizon. PDT was shown to be cost effective versus usual/best supportive care or no treatment in five of nine studies; two studies showed that PDT was of borderline cost effectiveness depending on baseline visual acuity, and two showed that PDT was not cost effective. We identified no robust studies that properly evaluated the cost effectiveness of bevacizumab in wet AMD.

PMID: 21244102 [PubMed - in process]

BMC Ophthalmol. 2011 Jan 17;11(1):1. [Epub ahead of print]

ISRCTN12125882 - Influence of topical anti-VEGF (Ranibizumab) on the outcome of filtration surgery for glaucoma- Study Protocol.

Bochmann F, Kaufmann C, Becht CN, Guber I, Kaiser M, Bachmann LM, Thiel MA.

ABSTRACT: Background Excessive wound healing, with scarring of the episcleral tissue or encapsulation of the filtering bleb is the main reason for failure in trabeculectomy. Ranibizumab, an inhibitor of the Vascular Endothelial Growth Factor (VEGF), is seen as a promising candidate to prevent or treat extensive wound healing. We describe the design of a two phased study, i) assessing the local tolerability and safety of topical ranibizumab and ii) assessing the efficacy of topical ranibizumab against placebo in patients who underwent trabelculectomy with mitomycin C combined with phacoemulsification and intra ocular lens (IOL) implantation. Methods /Design In the first phase five patients that had trabeculectomy with mitomycin C combined with phacoemulsification and IOL implantation will be treated with topical ranibizumab (Lucentis) eye drops (2mg/ml) four times daily for one month. The treatment will be started at the first postoperative day. Patients will be assessed for local and systemic side effects using a standardised schedule. In the

second phase, after successful completion of phase 1, consenting eligible patients who underwent trabelculectomy with mitomycin C combined with phacoemulsification and IOL implantation will be randomised to either receive topical ranibizumab eyedrops (2mg/ml) four times daily for 1 month or placebo (BSS 4x/d for 1 month). Patients will be reviewed weekly for 4 weeks until conjunctival sutures are removed. Further follow up examinations are planned after 3 and six months. Assessment of differences in the intraocular eye pressure will be considered primary, and bleb appearance / vascularisation using a standardized photography and the Moorfields bleb grading system, postoperative intraocular pressure and conjunctival wound healing problems will be considered secondary outcome parameters. Discussion Anti-VEGF-antibodies might be more effective in preventing scaring and might have fewer toxic side effects than the currently used anti-metabolites and may replace them in the long term. Trial Registration: ISRCTN12125882.

PMID: 21241468 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Eye (Lond). 2011 Jan 21. [Epub ahead of print]

Development of polypoidal lesions in age-related macular degeneration.

Tsujikawa A, Ojima Y, Yamashiro K, Ooto S, Tamura H, Nakata I, Yoshimura N.

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Purpose: To investigate the development of polypoidal lesions using indocyanine green angiography (IA) in eyes with typical age-related macular degeneration (AMD).

Methods: We retrospectively reviewed the medical records of 47 consecutive patients (47 eyes) with typical AMD who had been followed up with IA for at least 2 years.

Results: At the initial visit, although all eyes showed classic and/or occult choroidal neovascularization (CNV) associated with AMD, no eyes showed polypoidal lesions by IA. However, during follow-up, 13 (27.7%) of the 47 eyes did show polypoidal lesions. All polypoidal lesions developed at the edge of persistent CNV or, more often, at the terminus of recently progressed CNV. Of 12 eyes with a final lesion area >8 disc area, 7 (58.3%) showed newly developed polypoidal lesions. In the eyes with these newly developed polypoidal lesions, the mean area of the vascular lesion had extended significantly from 10.50±7.88 mm(2) to 20.87±10.21 mm(2) during follow-up (P=0.0018).

Conclusion: The current observation suggests that IA of active AMD sometimes reveals polypoidal lesions if there is progression of the CNV in the subretinal pigment epithelium space. Eye advance online publication, 21 January 2011; doi:10.1038/eye.2010.232.

PMID: 21252945 [PubMed - as supplied by publisher]

Int J Alzheimers Dis. 2011 Jan 5;2010:793931.

Alzheimer's disease and glaucoma: imaging the biomarkers of neurodegenerative disease.

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Imaging through the visual system in Alzheimer's disease, with the technology currently in widespread use for the diagnosis and management of eye disease such as glaucoma and macular degeneration, is proving to be promising. In vivo cross-section imaging during an annual comprehensive eye exam has been

available for a decade for glaucoma and macular degeneration, and this same imaging, using Optical Coherence Tomography, has been demonstrated to show deficits specific to AD and mild cognitive impairment. These deficits are in the form of nerve fiber layer tissue drop out in the retina and optic nerve. The retrograde loss of nerve fiber layer tissue in the retina and optic nerve may be an early biomarker of AD, and these deficits in the nerve fiber layer of the retina and optic nerve may be the earliest sign of AD, even prior to damage to the hippocampal region that impacts memory.

PMID: 21253485 [PubMed - in process]

Genetics

Hum Mol Genet. 2011 Jan 20. [Epub ahead of print]

Risk and non risk associated variants at the 10q26 AMD locus influence ARMS2 mRNA expression but exclude pathogenic effects due to protein deficiency.

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Abstract

Fifteen variants in 10q26 are in strong linkage disequilibrium and are associated with an increased risk for age related macular degeneration (AMD), a frequent cause of blindness in developed countries. These variants tag a single risk haplotype encompassing the genes ARMS2 (age-related maculopathy susceptibility 2) and part of HTRA1 (HtrA serine peptidase 1). To define the true AMD susceptibility gene in 10q26, several studies have focused on the influence of risk alleles on the expression of ARMS2 and/or HTRA1, but the results have been inconsistent. By heterologous expression of genomic ARMS2 variants, we now show that ARMS2 mRNA levels transcribed from the risk haplotype are significantly reduced compared to non-risk mRNA isoforms. Analyzing variant ARMS2 constructs, this effect could specifically be assigned to the known insertion/deletion (indel) polymorphism (c.(*)372_815del443ins54) in the 3'-UTR of ARMS2. Reporter gene assays with HTRA1 promoter sequences demonstrated the presence of a Müller glia-specific cis-regulatory region further upstream of the transcription start site. However, AMD risk alleles had little or no effect on HTRA1 promoter activity in the retina. Analysis of a large series of human post mortem retina/RPE samples heterozygous for the risk haplotype confirmed the in vitro/ex vivo results and demonstrated that the risk haplotype affects ARMS2 but not HTRA1 mRNA expression. Furthermore, we provide in vivo evidence that a common non risk associated non-synonymous variant (rs2736911) also leads to decreased ARMS2 transcript levels. Consequently, our data suggest that pathogenic effects due to ARMS2 protein deficiency are unlikely to account for AMD pathology.

PMID: 21252205 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2011 Jan 12. [Epub ahead of print]

Polymorphisms in ARMS2 (LOC387715) and LOXL1 Genes in Japanese with Age-Related Macular Degeneration.

Fuse N, Mengkegale M, Miyazawa A, Abe T, Nakazawa T, Wakusawa R, Nishida K.

PURPOSE: To determine whether polymorphisms in the ARMS2 (LOC387715) gene and the lysyl oxidase-like 1 (LOXL1) gene are associated with age-related macular degeneration (AMD) in Japanese patients.

DESIGN: Clinically relevant laboratory investigation.

METHODS: Forty-one unrelated Japanese subjects with dry AMD, 50 subjects with exudative (wet) AMD,

and 60 subjects with polypoidal choroidal vasculopathy (PCV) were studied. The single nucleotide polymorphisms (SNPs), p.Ala69Ser of the ARMS2 gene and p.Arg141Leu of the LOXL1 gene, were amplified by polymerase chain reaction, directly sequenced, and genotyped.

RESULTS: For the ARMS2 gene, the genotype frequency of the p.Ala69Ser single nucleotide polymorphism in eyes with dry AMD was not significantly different from that in the controls (P = .04), but the frequency was significantly higher in the exudative AMD group (P = 3.1 × 10(-8)) and PCV group (P = 6.9 × 10(-3)). For the LOXL1 gene, the genotype frequency of the p.Arg141Leu single nucleotide polymorphism was not statistically higher in the dry AMD and PCV groups than in the control group (dry AMD, P = .05; PCV, P = .16), but was statistically higher in the exudative AMD group (P = 6.8 × 10(-3)). Regression analyses showed significant associations between the ARMS2 gene and LOXL1 gene in patients with exudative AMD.

CONCLUSIONS: The p.Ala69Ser polymorphism of the ARMS2 gene is strongly associated with exudative AMD and PCV and is associated marginally with dry AMD. The polymorphisms in the LOXL1 gene did not predispose the individual to dry AMD and PCV. These findings suggest that there is a significant association between the ARMS2 gene and LOXL1 gene in exudative AMD.

PMID: 21236409 [PubMed - as supplied by publisher]

Epidemiology and pathogenesis

Mol Vis. 2011 Jan 10;17:85-98.

SU5416 induces premature senescence in endothelial progenitor cells from patients with age-related macular degeneration.

Thill M, Berna MJ, Kunst F, Wege H, Strunnikova NV, Gordiyenko N, Grierson R, Richard G, Csaky KG.

PURPOSE: We recently demonstrated increased frequency and growth potential of late outgrowth endothelial progenitor cells (OECs) in patients with neovascular age-related macular degeneration (nvAMD). This study investigated the effects of short- and long-term in vitro inhibition of vascular endothelial growth factor (VEGF) Receptor-2 (VEGFR-2) signaling by SU5416 and other inhibitors of the VEGF signaling pathway in OECs.

METHODS: OECs, from the peripheral blood of patients with nvAMD, and human umbilical vein endothelial cells were grown in the presence of SU5416, other VEGFR-2 tyrosine kinase inhibitors (TKIs), and inhibitors of phosphatidylinositol 3'-Kinase (PI3K)/protein kinase B (Akt) and protein kinase C (PKC) in complete angiogenic medium. Apotosis was assessed after 48 h using the fluorescein isothiocyanate Annexin V method. Cell counts were performed for 10 days, and features of senescence were analyzed using senescence-associated β-galactosidase staining, the telomeric repeat amplification protocol for telomerase activity, Southern blot analysis for mean telomere length, flow cytometric analysis for cell-cycle arrest, and western blot for p53 and p21. Control OECs, cells treated for 7 days with inhibitors, as well as naturally senescent OECs were analyzed for expression of different endothelial antigens, including VEGFR-2 and the receptor for stromal cell-derived factor 1, chemokine receptor 4 (CXCR-4). Migration in vitro to VEGF and stromal cell-derived factor 1 of OECs was assessed.

RESULTS: SU5416, other VEGFR-2 TKIs, and inhibitors of PI3K, Akt, and PKC induced apoptosis, inhibited long-term proliferation, reduced telomerase activity, and induced premature senescence and cell-cycle arrest in OECs as well as in human umbilical vein endothelial cells. Naturally senescent cells and cells rendered senescent by VEGFR-2 TKIs had reduced VEGFR-2 and CXCR-4 expression and demonstrated reduced migratory ability to VEGF.

CONCLUSIONS: This study demonstrates apoptosis upon short-term inhibition and inhibition of long-term survival of OECs from patients with nvAMD by SU5416, presumably via PI3K/Akt and/or PKC-mediated reduction in telomerase activity and subsequent induction of premature senescence, which is accompanied

by impaired endothelial activity. Therefore, induction of premature senescence in endothelial cells may represent a potential therapeutic target in nvAMD.

PMID: 21245959 [PubMed - in process]

Mol Endocrinol. 2011 Jan 14. [Epub ahead of print]

Research Resource: Nuclear Receptor Atlas of Human Retinal Pigment Epithelial Cells: Potential Relevance to Age-Related Macular Degeneration.

Dwyer MA, Kazmin D, Hu P, McDonnell DP, Malek G.

Department of Pharmacology and Cancer Biology (M.A.D., D.K., D.P.M.), Albert Eye Research Institute (P.H., G.M.), and Departments of Ophthalmology (P.H., G.M.) and Pathology (G.M.), Duke University, Durham, North Carolina 27710.

Abstract

Retinal pigment epithelial (RPE) cells play a vital role in retinal physiology by forming the outer blood-retina barrier and supporting photoreceptor function. Retinopathies including age-related macular degeneration (AMD) involve physiological and pathological changes in the epithelium, severely impairing the retina and effecting vision. Nuclear receptors (NRs), including peroxisome proliferator-activated receptor and liver X receptor, have been identified as key regulators of physiological pathways such as lipid metabolic dysregulation and inflammation, pathways that may also be involved in development of AMD. However, the expression levels of NRs in RPE cells have yet to be systematically surveyed. Furthermore, cell culture lines are widely used to study the biology of RPE cells, without knowledge of the differences or similarities in NR expression and activity between these in vitro models and in vivo RPE. Using quantitative real-time PCR, we assessed the expression patterns of all 48 members of the NR family plus aryl hydrocarbon receptor and aryl hydrocarbon receptor nuclear translocator in human RPE cells. We profiled freshly isolated cells from donor eyes (in vivo), a spontaneously arising human cell line (in vitro), and primary cell culture lines (in vitro) to determine the extent to which NR expression in the cultured cell lines reflects that of in vivo. To evaluate the validity of using cell culture models for investigating NR receptor biology, we determined transcriptional activity and target gene expression of several moderately and highly expressed NRs in vitro. Finally, we identified a subset of NRs that may play an important role in pathobiology of AMD.

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Pre-clinical

Ophthalmologe. 2011 Jan 21. [Epub ahead of print]

[Cytoprotective and antiangiogenic effects of the multikinase inhibitor sorafenib on human retinal pigmentepithelium.]

[Article in German]

Kernt M, Thiele S, Hirneiss C, Neubauer AS, Lackerbauer CA, Wolf A, Eibl KH, Haritoglou C, Ulbig MW, Kampik A.

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BACKGROUND: Cumulative light exposure is significantly associated with progression of age-related macular degeneration (AMD). Inhibition of vascular endothelial growth factor A (VEGF) is the main target of current antiangiogenic treatment strategies for AMD. Previous reports indicated that sorafenib, an oral multikinase inhibitor, might have beneficial effects on exudative AMD. This study investigates the effects of

sorafenib on light-induced overexpression of VEGF and its receptors VEGFR1 and 2 in human retinal pigment epithelial (RPE) cells.

METHODS: The effects of sorafenib on VEGFR1 and 2 expression of primary human RPE cells was investigated by reverse transcription polymerase chain reaction (RT-PCR), immunohistochemistry and western blotting. In addition, RPE cells were exposed to white light and incubated with sorafenib. Viability, expression of VEGF and its mRNA were determined by RT-PCR, immunohistochemistry, western blotting, and enzyme-linked immunosorbent assays.

RESULTS: Sorafenib reduced VEGFR1 and 2 expression of RPE cells. Light exposure decreased cell viability and increased expression and secretion of VEGF. These light-induced effects were significantly reduced when cells were treated with sorafenib at a dose of 1 μg/ml.

CONCLUSION: The results show that sorafenib has promising properties as a potential antiangiogenic treatment for AMD.

PMID: 21253747 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Jan 18. [Epub ahead of print]

Naloxone Ameliorates Retinal Lesions in Ccl2/Cx3cr1 Double Deficient Mice via Modulation of Microglia.

Shen D, Cao X, Zhao L, Tuo J, Wong WT, Chan CC.

Immunopathology Section, Laboratory of Immunology.

Purpose The role of naloxone, an opioid receptor antagonist, on microglial inhibition and neuroprotective effects has been reported in LPS-induced neurodegeneration and light-induced photoreceptor degeneration. We evaluated the effects of naloxone on Ccl2(-/-)/Cx3cr1(-/-) (DKO) mice, a murine model of age-related macular degeneration (AMD). Methods Two-month old DKO and wild type controls were given daily intraperitoneal injections of naloxone or PBS for two months. Animals were examined monthly by funduscopy. Ocular tissue was analyzed histologically and in retinal flat-mount preparations. Ocular A2E was measured using HPLC. Quantitative RT-PCR analyzed TNF-α, IL-1β, IL-10 and TLR4 transcripts in the DKO eyes and LPS activated culture microglial cells. Serum nitrite was measured using Griess colorimetric reaction. Results Naloxone ameliorated clinical progression and severity of retinal lesions in the DKO mice compared to those untreated controls. Histopathology also showed less focal retinal degeneration in the treated DKO mice compared to controls. The aggregation of microglia in the outer retina in DKO mice was significantly reduced in naloxone-treated animals compared to control untreated DKO. Ocular TNF-α, IL-1β and TLR4 transcripts and A2E were significantly lower in naloxone-treated DKO animals and cultured microglial cells compared to controls, as were serum nitrite levels. Conclusion Naloxone significantly reduces the progress of retinal lesions in DKO mice. Naloxone modulates microglia accumulation and activation at the site of retinal degeneration, which may be mediated via inhibition of pro-inflammatory molecules of NO, TNF-α and IL-β. The potential therapeutic effects of naloxone on retinal degeneration including AMD, warrants further investigation.

PMID: 21245403 [PubMed - as supplied by publisher]

Diet & Lifestyle

Invest Ophthalmol Vis Sci. 2011 Jan 18. [Epub ahead of print]

Nutritional Manipulation of Primate Retinas. V: Effects of Lutein, Zeaxanthin and n--3 Fatty Acids on Retinal Sensitivity to Blue Light Damage.

Barker FM 2nd, Snodderly DM, Johnson EJ, Schalch W, Koepcke W, Gerss J, Neuringer M.

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Purpose: Blue light photooxidative damage has been implicated in the etiology of age-related macular degeneration (AMD). The macular pigment xanthophylls lutein (L) and zeaxanthin (Z) and n--3 fatty acids may reduce this damage and lower AMD risk. We investigated effects of lifelong absence of xanthophylls followed by L or Z supplementation, combined with effects of n--3 fatty acid deficiency, on acute blue light photochemical damage.

Methods: Subjects included eight rhesus monkeys with no lifelong intake of xanthophylls and no detectable macular pigment. Of these, four had low n--3 fatty acid intake and four had adequate intake. Controls had typical L, Z, and n--3 fatty acid intake. Retinas received 150 μm-diameter exposures of low-power 476 nm laser light either at 0.5 mm (~2(o)) eccentricity, adjacent to the macular pigment peak, or parafoveally at 1.5 mm (~6(o)). Exposures of xanthophyll-free animals were repeated after supplementation with pure L or Z for 22-28 weeks. Ophthalmoscopically visible lesion areas were plotted as a function of exposure energy, with greater slopes of the regression lines indicating greater sensitivity to damage.

Results: In control animals, the fovea was less sensitive to blue light damage than the parafovea. Foveal protection was absent in xanthophyll-free animals but evident after supplementation. In the parafovea, animals low in n--3 fatty acids showed greater sensitivity to damage than animals with adequate levels.

Conclusions: After long-term xanthophyll deficiency, L or Z supplementation protected the fovea from blue light damage, whereas adequate n--3 fatty acid levels reduced damage in the parafovea.

PMID: 21245404 [PubMed - as supplied by publisher]

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