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Drug treatment

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Time to Clinically Significant Visual Acuity Gains after Ranibizumab Treatment for Retinal Vein Occlusion: BRAVO and CRUISE Trials.

Thach AB, Yau L, Hoang C, Tuomi L.

PURPOSE: To assess time to first achievement of clinically significant visual acuity (VA) gains from baseline in patients with retinal vein occlusion (RVO) receiving ranibizumab versus sham treatment.

DESIGN: Post hoc analyses of 2 phase 3 clinical trials assessing efficacy and safety of ranibizumab in patients with branch RVO (Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety [BRAVO] study; NCT00061594) and central RVO (Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety [CRUISE]; NCT00056836) over 12 months.

PARTICIPANTS: Seven hundred eighty-nine patients (BRAVO, n = 397; CRUISE, n = 392).

INTERVENTION: Randomization to monthly intraocular ranibizumab injections (0.3 mg/0.5 mg) or sham. After 6 monthly injections (treatment period), patients meeting prespecified criteria received as-needed (pro re nata [PRN]) ranibizumab at their assigned dose (sham patients, ranibizumab 0.5 mg) through month 12 (observation period). BRAVO patients meeting specific eligibility criteria could receive rescue laser treatment once during the treatment and once during the observation periods.

MAIN OUTCOME MEASURES: Time to first gain of 15 letters or more from baseline, analyzed using Kaplan-Meier methods. To evaluate the effect of delaying ranibizumab treatment, sham patients' VA data also were analyzed, with month 6 considered as baseline to assess vision gains during the 6 months of receiving ranibizumab PRN.

RESULTS: Median time to first 15-letter or more gain from baseline was 12.0 (sham), 4.8 (ranibizumab 0.3 mg), and 4.0 months (ranibizumab 0.5 mg) in BRAVO and 12.2, 5.9, and 5.2 months, respectively, in CRUISE. The cumulative proportion of patients who had ever gained 15 letters or more from baseline by month 12 was 50% (sham), 68% (ranibizumab 0.3 mg), and 71% (ranibizumab 0.5 mg) in BRAVO and 42%, 61%, and 66%, respectively, in CRUISE. After 6 months of ranibizumab PRN treatment, a cumulative 10.8% (BRAVO) and 26.2% (CRUISE) of initially sham-treated patients ever gained 15 letters or more.

CONCLUSIONS: This retrospective analysis shows that more than 50% of patients treated with monthly ranibizumab achieved clinically significant vision gains during the initial 6 months of treatment, which largely

were maintained using PRN treatment to 12 months. In comparison, less than 50% of patients initially randomized to sham (and later receiving ranibizumab 0.5 mg PRN treatment) ever achieved clinically significant vision gains. These results suggest that initiating treatment immediately after diagnosis may provide the greatest vision gains. The potential benefits of early treatment should be evaluated further in prospective clinical studies.

PMID: 24424249 [PubMed - as supplied by publisher]

Semin Ophthalmol. 2014 Jan 10. [Epub ahead of print]

Ranibizumab Treatment for Choroidal Neovascularization Secondary to Causes Other than Age-Related Macular Degeneration with Good Baseline Visual Acuity.

Erol MK, Ozdemir O, Coban DT, Ceran BB, Bulut M.

Purpose: To report a retrospective series of choroidal neovascularization (CNV) patients treated with intravitreal ranibizumab with good baseline vision from causes other than age-related macular degeneration (AMD).

Methods: We retrospectively reviewed 12 eyes of 12 patients with CNV secondary to non-AMD who received intravitreal ranibizumab injections. Patients with baseline best-corrected visual acuity (BCVA) above 20/63 were included in the study. All patients were followed up at least for 12 months. BCVA measurement, fundus examination, and OCT examination of the patients were performed at each visit. Optical coherence tomography (OCT), fundus photo, fundus autofluorescence, and fundus fluorescein angiography examination of the eyes were obtained. Primary outcome measures were the changing in BCVA and central foveal thickness (CFT). Any ocular or systemic side-effects were recorded.

Results: The ages of patients ranged from 17 to 60. Twelve patients were diagnosed with non-AMD associated CNV: myopia (n = 3), central serous chorioretinopathy (n = 3), idiopathic (n = 2), multifocal choroiditis (n = 2), punctate inner choroidopathy (n = 1), and photo toxicity (n = 1). The improvement in visual acuity was statistically significant (p = 0.001). In the 12-month visit, all eyes had improvement in visual acuity except two eyes. The reduction of the mean CFT was statistically significant (p = 0.001). The CFT of all patients decreased in the 12-month visit. There was no significant difference in comparison of the mean intraocular pressure (p = 0.790). The group received a total of 52 intravitreal injections. The mean number of intravitreal injections was 4.3 (ranged from 3-8).

Conclusion: Ranibizumab seems to be an effective and safe treatment option for CNVs secondary to non-AMD causes in patients with relatively good baseline BCVAs.

PMID: 24409939 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2014 Jan 15. [Epub ahead of print]

Efficacy of treatment with ranibizumab in patients with wet age-related macular degeneration in routine clinical care: data from the COMPASS health services research.

Wolf A, Kampik A.

BACKGROUND: To assess healthcare processes during treatment of neovascular age-related macular degeneration (AMD) in patients under real-life conditions and evaluate efficacy of monthly visual acuity (VA) assessment in a pro re nata treatment regime.

METHODS: A multicentre, prospective, non-interventional study based in Germany included neovascular AMD patients treated with intravitreal ranibizumab. Patients completed a 3-month loading phase with monthly intravitreal injections of 0.5 mg ranibizumab, followed by a 12-month maintenance phase during

which investigators documented VA, additional injections, metamorphopsias, routine ophthalmological examinations and adverse events at monthly follow-up visits. Efficacy analysis included change from baseline in best-corrected VA (BCVA) based on descriptive statistics.

RESULTS: A total of 2,232 patients were enrolled throughout Germany and 1,729 patients (mean age 77.8 years, 63.2 % women) comprised the efficacy population with a complete set of data. In the clinical setting recorded in our study, only a minority of patients underwent optical coherence tomography during the maintenance phase (71 of 1,729 patients). Patients received a mean total of 4.5 injections; three injections during upload phase and 1.5 additional injections during maintenance phase. Over half of the patients (51.4 %) did not receive additional injections. Mean decimal BCVA increased during the upload phase, (from LogMAR mean of 0.201 at baseline to 0.219 at Month 4) but displayed a decline over time (0.192 at Month 15).

CONCLUSION: Ranibizumab treatment in a real-life setting demonstrated efficacy in neovascular AMD patients, as shown by initial gains in BCVA. However, maintenance and improvement of these gains during the maintenance phase in a clinical routine setting remained below those expected compared with MARINA, ANCHOR and CATT trials, most likely due to a low number of retreatments, and the high number of patients with a poor response in regard to improvements of VA who were not investigated in these studies.

PMID: 24424409 [PubMed - as supplied by publisher]

Mol Vis. 2014 Jan 6;20:46-55. eCollection 2014.

Age-related macular degeneration: Beyond anti-angiogenesis.

Kent DL.

Abstract: Recently, anti-vascular endothelial growth factor therapies for neovascular age-related macular degeneration have been developed. These agents, originally developed for their anti-angiogenic mechanism of action, probably also work through an anti-permeability effect in preventing or reducing the amount of leakage from submacular neovascular tissue. Other treatment modalities include laser photocoagulation, photodynamic therapy with verteporfin, and submacular surgery. In reality, these latter treatments can be similarly categorized as anti-angiogenic because their sole aim is destroying or removing choroidal neovascularization (CNV). At the cellular level, CNV resembles stereotypical tissue repair that consists of several matricellular components in addition to neovascularization. In the retina, the clinical term CNV is a misnomer since the term may more appropriately be referred to as aberrant submacular repair. Furthermore, CNV raises a therapeutic conundrum: To complete or correct any reparative process in the body, angiogenesis becomes an essential component. Anti-angiogenic therapy, in all its guises, arrests repair and causes the hypoxic environment to persist, thus fueling pro-angiogenesis and further development of CNV as a component of aberrant repair. However, we realize that anti-vascular endothelial growth factor therapy preserves vision in patients with age-related macular degeneration, albeit temporarily and therefore, repeated treatment is needed. More importantly, however, anti-angiogenic therapy demonstrates that we can at the very least tolerate neovascular tissue beneath the macula and preserve vision in contrast to our historical approach of total vascular destruction. In this clinical scenario, it may be possible to look beyond anti-angiogenesis if our goal is facilitating submacular repair without destroying the neurosensory retina. Thus, in this situation of neovascular tolerance, it may be timely to consider treatments that facilitate vascular maturation, rather than its arrest or destruction. This would neutralize hypoxia, thus removing the stimulus that drives neovascularization and in turn the need for repeated lifelong intravitreal therapy. A pro-angiogenic approach would eliminate neovascular leakage and ultimately complete repair and preserve the neurosensory retina.

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Cochrane Database Syst Rev. 2014 Jan 15;1:CD009300. [Epub ahead of print]

Complement inhibitors for age-related macular degeneration.

Williams MA, McKay GJ, Chakravarthy U.

BACKGROUND: Given the relatively high prevalence of age-related macular degeneration (AMD) and the increased incidence of AMD as populations age, the results of trials of novel treatments are awaited with much anticipation. The complement cascade describes a series of proteolytic reactions occurring throughout the body that generate proteins with a variety of roles including the initiation and promotion of immune reactions against foreign materials or micro-organisms. The complement cascade is normally tightly regulated, but much evidence implicates complement overactivity in AMD and so it is a logical therapeutic target in the treatment of AMD.

OBJECTIVES: To assess the effects and safety of complement inhibitors in the prevention or treatment of advanced AMD.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2013, Issue 11), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to November 2013), EMBASE (January 1980 to November 2013), Allied and Complementary Medicine Database (AMED) (January 1985 to November 2013), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to November 2013), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), Web of Science Conference Proceedings Citation Index - Science (CPCI-S) (January 1990 to November 2013), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 21 November 2013. We also performed handsearching of proceedings, from 2012 onwards, of meetings and conferences of specific professional organisations.

SELECTION CRITERIA: We planned to include randomised controlled trials (RCTs) with parallel treatment groups which investigated either the prevention or treatment of advanced AMD by inhibition of the complement cascade.

DATA COLLECTION AND ANALYSIS: Two authors (MW and GMcK) independently evaluated all the titles and abstracts resulting from the searches. We contacted companies running clinical trials which had not yet reported results to request information. Since no trials met our inclusion criteria, we undertook no assessment of quality or meta-analysis.

MAIN RESULTS: We identified and screened 317 references but there were no published RCTs that met the inclusion criteria. We identified two ongoing studies: one phase I study and one phase II study.

AUTHORS' CONCLUSIONS: There is insufficient information at present to generate evidence-based recommendations on the potential safety and efficacy of complement inhibitors for prevention or treatment of AMD. However we anticipate the results of ongoing trials.

PMID: 24431152 [PubMed - as supplied by publisher]

J Med Assoc Thai. 2013 Nov;96(11):1483-90.

The use of intravitreal anti-vascular endothelial growth factor injection and its complications in Chiang Mai University Hospital.

Kunavisarut P, Saenpen N, Ittipunkul N, Patikulsila D, Choovuthayakorn J, Watanachai N, Pathanapitoon K.

OBJECTIVE: To report the use of intravitreal (IVT) injections of anti-vascular endothelial growth factor agents (anti-VEGF) and its complications.

MATERIAL AND METHOD: The authors performed a retrospective review of consecutive patients treated with IVT injection of anti-VEGF between May 2006 and December 2010 at Chiang Mai University Hospital. Demographic data and complications were registered.

RESULTS: The present study included 1,006 eyes of 878 patients. Mean age was 60 years (range 1 month to 91 years). Mean follow-up time was 12 months (range 1 month to 54 months). Total injections were 2,077 given as 47, 210, 399, 575, and 846 injection per year between 2006 and 2010, respectively. Anti-VEGF agents were bevacizumab (1,878; 90.42%), ranibizumab (190; 9.15%), and pegaptanib (9; 0.43%). Indications for injection based on primary diagnosis were neovascular macular degeneration (38.5%), diabetic retinopathy (38%), and retinal vein occlusion (15.9%). The incidence of endophthalmitis was 0.048% (1/2,077) for all injections and 0.053% (1/1878)for bevacizumab.

CONCLUSION: The use of IVT injections of anti-VEGF is increasing, especially the use of bevacizumab. Incidence of ocular and systemic complications after IVT injection of anti- VEGF was low with no significant difference among the three anti-VEGFs agents.

PMID: 24428099 [PubMed - in process]

Other treatment & diagnosis

Ophthalmology. 2014 Jan 13. pii: S0161-6420(13)01102-0. doi: 10.1016/j.ophtha.2013.11.023. [Epub ahead of print]

Geographic Atrophy: Clinical Features and Potential Therapeutic Approaches.

Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M.

Abstract: In contrast to wet age-related macular degeneration (AMD), where loss of vision is typically acute and treatment leads to a relatively rapid reduction in retinal fluid and subsequent improvements in visual acuity (VA), disease progression and vision loss in geographic atrophy (GA) owing to AMD are gradual processes. Although GA can result in significant visual function deficits in reading, night vision, and dark adaptation, and produce dense, irreversible scotomas in the visual field, the initial decline in VA may be relatively minor if the fovea is spared. Because best-corrected VA does not correlate well with GA lesions or progression, alternative clinical endpoints are being sought. These include reduction in drusen burden, slowing the enlargement rate of GA lesion area, and slowing or eliminating the progression of intermediate to advanced AMD. Among these considerations, slowing the expansion of the GA lesion area seems to be a clinically suitable primary efficacy endpoint. Because GA lesion growth is characterized by loss of photoreceptors, it is considered a surrogate endpoint for vision loss. Detection of GA can be achieved with a number of different imaging techniques, including color fundus photography, fluorescein angiography, fundus autofluorescence (FAF), near-infrared reflectance, and spectral-domain optical coherence tomography. Previous studies have identified predictive characteristics for progression rates including abnormal patterns of FAF in the perilesional retina. Although there is currently no approved or effective treatment to prevent the onset and progression of GA, potential therapies are being evaluated in clinical studies.

PMID: 24433969 [PubMed - as supplied by publisher]

Biotechnol Adv. 2014 Jan 8. pii: S0734-9750(14)00002-0. doi: 10.1016/j.biotechadv.2014.01.001. [Epub ahead of print]

Advances in repairing the degenerate retina by rod photoreceptor transplantation.

Pearson RA.

Abstract: Despite very different aetiologies, age-related macular degeneration (AMD) and most inherited retinal disorders culminate in the same final common pathway, loss of the light-sensitive photoreceptors. There are few clinical treatments and none can reverse the loss of vision. Photoreceptor replacement by transplantation is proposed as a broad treatment strategy applicable to all degenerations. The past decade has seen a number of landmark achievements in this field, which together provide strong justification for continuing investigation into photoreceptor replacement strategies. These include proof of principle for restoring vision by rod-photoreceptor transplantation in mice with congenital stationary night blindness and advances in stem cell biology, which have led to the generation of complete optic structures in vitro from embryonic stem cells. The latter represents enormous potential for generating suitable and renewable donor cells with which to achieve the former. However, there are still challenges presented by the degenerating recipient retinal environment that must be addressed as we move to translating these technologies towards clinical application.

PMID: 24412415 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Jan 9. pii: S0002-9394(14)00009-9. doi: 10.1016/j.ajo.2013.12.029. [Epub ahead of print]

Assessment of choroidal topographic changes by swept source optical coherence tomography after photodynamic therapy for central serous chorioretinopathy.

Razavi S1, Souied EH2, Cavallero E2, Weber M3, Querques G4.

PURPOSE: To investigate the relationship between choroidal thickness and angiographic abnormalities in central serous chorioretinopathy (CSC) eyes by swept-source optical coherence tomography (Swept-OCT), before and after half-fluence photodynamic therapy (PDT).

DESIGN: Prospective interventional case series.

METHODS: Consecutive patients presenting with treatment-naïve active CSC underwent a complete ophthalmologic examination, including Swept-OCT at study entry, and 7 days and 30 days after treatment with half-fluence PDT. Main outcome measures were changes in choroidal maps after PDT (mean±SD) and the relationship between choroidal thickness and angiographic abnormalities.

RESULTS: Twelve eyes of 12 patients (2 females, 10 males; mean age 55.6±14.0 years) were included. At study entry, mean choroidal thickness measured in the center of the fovea was significantly thicker in the study eyes as compared to the fellow eyes (420.7±107.5 μm vs 349.2±109.7 μm, respectively; p=0.016). Mean choroidal thickness in the center of the fovea significantly decreased in the study eyes at both 7 days (380.2±113 μm; p=0.005) and 30 days after PDT (362.3±111 μm; p=0.002). A similar significant choroidal thinning was recorded in each ETDRS applied to 3D Swept-OCT maps. At each time-point, mean choroidal thickness was significantly thicker in sectors with than without angiographic abnormalities (421±102.4 μm vs. 397.6±96.5 μm, p=0.002 at study entry; 381.2±106.6 μm vs. 364±101.2 μm, p=0.01 at day-7; 366.3±103.2 μm vs. 347.2±99.6 μm at day-30).

CONCLUSIONS: Using Swept-OCT we demonstrated that in active CSC, choroidal thickness is increased to a greater extent in areas characterized by angiographic abnormalities. This increased choroidal thickness may persist even after PDT.

PMID: 24412124 [PubMed - as supplied by publisher]

Med Hypotheses. 2013 Dec 26. pii: S0306-9877(13)00593-8. doi: 10.1016/j.mehy.2013.12.009. [Epub ahead of print]

Protein conformational modulation by photons: A mechanism for laser treatment effects.

Liebert AD1, Bicknell BT2, Adams RD3.

Abstract: Responsiveness to low-level laser treatment (LLTT) at a wavelength of 450-910nm has established it as an effective treatment of medical, veterinary and dental chronic pain, chronic inflammation conditions (arthritis and macular degeneration), wound repair, and lymphoedema, yet the mechanisms underlying the effectiveness of LLLT remain unclear. However, there is now sufficient evidence from recent research to propose an integrated model of LLLT action. The hypothesis presented in this paper is that external applications of photons (through laser at an appropriate dose) modulates the nervous system through an integrated mechanism. This stimulated mechanism involves protein-to-protein interaction, where two or more proteins bind together to facilitate molecular processes, including modification of proteins by members of SUMO (small ubiquitin-related modifier proteins) and also protein phosphorylation and tyrosination. SUMO has been shown to have a role in multiple nuclear and perinuclear targets, including ion channels, and in the maintenance of telomeres and the post-translational modification of genes. The consequence of laser application in treatment, therefore, can be seen as influencing the transmission of neural information via an integrated and rapid modulation of ion channels, achieved through both direct action on photo-acceptors (such as cytochrome c-oxidase) and through indirect modulation via enzymes, including tyrosine hydroxylase (TH), tyrosine kinases and tyrosine kinase receptors. This exogenous action then facilitates an existing photonic biomodulation mechanism within the body, and initiates ion channel modulation both in the periphery and the central nervous system (CNS). Evidence indicates that the ion channel modulation functions predominately through the potassium channels, including two pore leak channels (K2P), which act as signal integrators from the periphery to the cortex. Photonic action also transforms SUMOylation processes at the cell membrane, nucleus and telomeres via signalling processes from the mitochondria (which is the main target of laser absorption) to these targets. Under the hypothesis, these observed biological effects would play a part in the bystander effect, the abscopal effect, and other systemic effects observed with the application of low level laser (LLLT). The implications of the hypothesis are important in that they point to mechanisms that can account for the effectiveness of laser in the treatment and prevention of inflammatory diseases, chronic pain and neurodegenerative disorders.

PMID: 24424395 [PubMed - as supplied by publisher]

Pathogenesis

Mol Vis. 2014 Jan 7;20:73-88.

L-2-oxothiazolidine-4-carboxylic acid attenuates oxidative stress and inflammation in retinal pigment epithelium.

Promsote W, Veeranan-Karmegam R, Ananth S, Shen D, Chan CC, Lambert NA, Ganapathy V, Martin PM.

PURPOSE: Oxidant- and inflammation-induced damage to retinal pigment epithelial (RPE) cells is central to the pathogenesis of age-related macular degeneration (AMD). Thus, developing novel strategies to protect these cells is important. We reported previously on the robust antioxidant and therefore cell-protective effects of the cysteine pro-drug L-2-oxothiazolidine-4-carboxylic acid (OTC) in cultured human RPE cells. New reports citing a novel anti-inflammatory role for OTC in addition to the known glutathione-stimulating and antioxidant properties emerged recently; however, this role has not been evaluated in RPE cells or in intact retina. Given the crucial causative roles of oxidative stress and inflammation in AMD pathogenesis, knowing whether OTC might exhibit a similar benefit in this cell and tissue type has high clinical relevance; thus, we evaluated OTC in the present study.

METHODS: ARPE-19 and primary RPE cells isolated from wild-type, Gpr109a(-/-) , or Slc5a8(-/-) mouse

eyes were exposed to TNF-α in the presence or absence of OTC, followed by analysis of IL-6 and Ccl2 expression with real-time quantitative polymerase chain reaction or enzyme-linked immunosorbent assay. Cellular and molecular markers of inflammation and oxidative stress (i.e., IL-1β, TGF-β, ABCG1, ABCA1, reduced glutathione, and dihydroethidium) were evaluated in Ccl2(-/-)/Cx3cr1(-/-) double knockout mice on rd8 background (DKO rd8) treated with OTC (10 mg/ml) in drinking water for a period of 5 months.

RESULTS: OTC treatment significantly inhibited the expression and secretion of IL-6 and Ccl2 in TNF-α-stimulated ARPE-19 cells. Studies conducted using DKO rd8 animals treated with OTC in drinking water confirmed these findings. Cellular and molecular markers of inflammation were significantly suppressed in the retinas of the OTC-treated DKO rd8 animals. Subsequent in vitro and in vivo studies of the possible mechanism(s) to explain these actions revealed that although OTC is an agonist of the anti-inflammatory G-protein coupled receptor GPR109A and a transportable substrate of the sodium-coupled monocarboxylate transporter SMCT1 (SLC5A8), these properties may play a role but do not explain entirely the anti-inflammatory effects this compound elicits in cultured RPE cells and the intact mouse retina.

CONCLUSIONS: This study represents, to our knowledge, the first report of the suppressive effects of OTC on inflammation in cultured RPE cells and on inflammation and oxidative stress in the retina in vivo.

PMID: 24426777 [PubMed - in process] PMCID: PMC3888500

Surv Ophthalmol. 2014 Jan 10. pii: S0039-6257(13)00210-5. doi: 10.1016/j.survophthal.2013.09.004. [Epub ahead of print]

Trophic factors in the pathogenesis and therapy for retinal degenerative diseases.

Kolomeyer AM, Zarbin MA.

Abstract: Trophic factors are endogenously secreted proteins that act in an autocrine and/or paracrine fashion to affect vital cellular processes such as proliferation, differentiation, and regeneration, thereby maintaining overall cell homeostasis. In the eye, the major contributors of these molecules are the retinal pigment epithelial (RPE) and Müller cells. The primary paracrine targets of these secreted proteins include the photoreceptors and choriocapillaris. Retinal degenerative diseases such as age-related macular degeneration and retinitis pigmentosa are characterized by aberrant function and/or eventual death of RPE cells, photoreceptors, choriocapillaris, and other retinal cells. We discuss results of in vitro and in vivo animal studies in which candidate trophic factors, either singly or in combination, were used in an attempt to ameliorate photoreceptor and/or retinal degeneration. We also examine current trophic factor therapies as they relate to the treatment of retinal degenerative diseases in clinical studies.

PMID: 24417953 [PubMed - as supplied by publisher]

Exp Eye Res. 2013 Nov;116:359-65.

Autophagy of iron-binding proteins may contribute to the oxidative stress resistance of ARPE-19 cells.

Karlsson M, Frennesson C, Gustafsson T, Brunk UT, Nilsson SE, Kurz T.

Abstract: The objective of this study was to elucidate possible reasons for the remarkable resistance of human retinal pigment epithelial (RPE) cells to oxidative stress. Much oxidative damage is due to hydrogen peroxide meeting redox-active iron in the acidic and reducing lysosomal environment, resulting in the production of toxic hydroxyl radicals that may oxidize intralysosomal content, leading to lipofuscin (LF) formation or, if more extensive, to permeabilization of lysosomal membranes. Formation of LF is a risk factor for age-related macular degeneration (AMD) and known to jeopardize normal autophagic rejuvenation of vital cellular biomolecules. Lysosomal membrane permeabilization causes release of

lysosomal content (redox-active iron, lytic enzymes), which may then cause cell death. Total cellular and lysosomal low-mass iron of cultured, immortalized human RPE (ARPE-19) cells was compared to that of another professional scavenger cell line, J774, using atomic absorption spectroscopy and the cytochemical sulfide-silver method (SSM). It was found that both cell lines contained comparable levels of total as well as intralysosomal iron, suggesting that the latter is mainly kept in a non-redox-active state in ARPE-19 cells. Basal levels and capacity for upregulation of the iron-binding proteins ferritin, metallothionein and heat shock protein 70 were tested in both cell lines using immunoblotting. Compared to J774 cells, ARPE-19 cells were found to contain very high basal levels of all these proteins, which could be even further upregulated following appropriate stimulation. These findings suggest that a high basal expression of iron-binding stress proteins, which during their normal autophagic turnover in lysosomes may temporarily bind iron prior to their degradation, could contribute to the unusual oxidative stress-resistance of ARPE-19 cells. A high steady state influx of such proteins into lysosomes would keep the level of lysosomal redox-active iron permanently low. This, in turn, should delay intralysosomal accumulation of LF in RPE cells, which is known to reduce autophagic turnover as well as uptake and degradation of worn out photoreceptor tips. This may explain why severe LF accumulation and AMD normally do not develop until fairly late in life, in spite of RPE cells being continuously exposed to high levels of oxygen and light, as well as large amounts of lipid-rich material.

PMID: 24416768 [PubMed - in process]

JAKSTAT. 2013 Oct 1;2(4):e25434. Epub 2013 Jun 17.

Signal transducer and activator of transcription 3 (STAT3) signaling in retinal pigment epithelium cells.

Patel AK, Syeda S, Hackam AS.

Abstract: The retinal pigmented epithelium (RPE) is a monolayer of specialized epithelial cells located between the photoreceptors of the retina and the choroidal blood supply. The RPE is essential for maintaining retinal health and vision. Recent findings identified STAT3 as a newly recognized regulator of RPE survival, inflammatory response, visual cycle maintenance, and cytokine release. Additionally, STAT3 is implicated in retinal diseases that affect the RPE, including the common blinding disease age-related macular degeneration. Determining how STAT3 influences RPE functions ultimately may lead to novel therapeutics for retinal disease. In this review, we summarize the roles of JAK-STAT3 signaling in the RPE, and its potential contribution to retinal degenerations.

PMID: 24416648 [PubMed - as supplied by publisher] PMCID: PMC3876436

Free Radic Biol Med. 2014 Jan 13. pii: S0891-5849(14)00005-7. doi: 10.1016/ j.freeradbiomed.2014.01.004. [Epub ahead of print]

Oxidative Stress Induces Mitochondrial Dysfunction and a Protective Unfolded Protein Response in RPE cells.

Cano M, Wang L, Wan J, Barnett BP, Ebrahimi K, Qian J, Handa JT.

Abstract: How cells degenerate from oxidative stress in aging-related disease is incompletely understood. The study's intent was to identify key cytoprotective pathways activated by oxidative stress, and determine the extent of their protection. Using an unbiased strategy with microarray analysis, retinal pigmented epithelial (RPE) cells treated with cigarette smoke extract (CSE) had over-represented genes involved in the antioxidant and unfolded protein response (UPR). Differentially expressed antioxidant genes were predominantly located in the cytoplasm, with no induction of genes that neutralize superoxide and H2O2 in the mitochondria, resulting in accumulation of superoxide and decreased ATP production. Simultaneously,

CSE induced the UPR sensors IRE1α, p-PERK, and ATP6, including CHOP, which was cytoprotective because CHOP knockdown decreased cell viability. In mice given intravitreal CSE, the RPE had increased IRE1α and decreased ATP, and developed epithelial-mesenchymal transition, as suggested by decreased LRAT abundance, altered ZO1 immunolabeling, and dysmorphic cell shape. Mildly degenerated RPE from early AMD samples had prominent IRE1α, but minimal mitochondrial TOM20 immunolabeling. While oxidative stress is thought to induce an antioxidant response with cooperation between the mitochondria and ER, herein, we show that mitochondria become impaired sufficiently to induce epithelial-mesenchymal transition despite a protective UPR. With similar responses in early AMD samples, these results suggest that mitochondria are vulnerable to oxidative stress despite a protective UPR during early phases of aging-related disease.

PMID: 24434119 [PubMed - as supplied by publisher]

J Clin Exp Ophthalmol. 2013 Oct 1;4(5):1000296.

Evaluating Potential Therapies in a Mouse Model of Focal Retinal Degeneration with Age-related Macular Degeneration (AMD)-Like Lesions.

Popp N, Chu XK, Shen D, Tuo J, Chan CC.

Abstract: Although the mouse has no macula leutea, its neuroretina and retinal pigment epithelium (RPE) can develop lesions mimicking certain features of age-related macular degeneration (AMD). Differences between the Ccl2 and Cx3cr1 double deficient mouse on Crb1rd8 (rd8) background (DKO rd8) and the Crb1rd8 mouse in photoreceptor and RPE pathology, as well as ocularA2E contents and immune responses, show that DKO rd8 recapitulates some human AMD-like features in addition to rd8 retinal dystrophy/degeneration. Different therapeutic interventions have been demonstrated to be effective on the AMD-like features of DKO rd8 mice. The use of the DKO rd8 model and C57BL/6N (wild type, WT) mice as group controls (4 groups) to test treatments such as high omega-3 polyunsaturated fatty acid (n-3) diet has, for example, shown the beneficial effect of n-3 on AMD-like lesions by anti-inflammatory action of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). The use of self-control in the DKO rd8 mouse by treating one eye and using the contralateral eye as the control for the same mouse allows for appropriate interventional experiments and evaluates various novel therapeutic agents. Three examples will be briefly presented and discussed: (1) tumor necrosis factor-inducible gene 6 recombinant protein (TSG-6) arrests the AMD-like lesions via modulation of ocular immunological gene expression, e.g., Il-17a; (2) adeno-associated virus encoding sIL-17R (AAV2.sIL17R) stabilizes the AMD-like lesions; and (3) pigment epithelium-derived factor (PEDF) ameliorates the AMD-lesions by its anti-inflammatory, anti-apoptotic and neuroprotective roles. Therefore, the DKO rd8 mouse model can be useful and appropriate for therapeutic compound screening in the management of human AMD.

PMID: 24432192 [PubMed]

Epidemiology

Clin Hemorheol Microcirc. 2014 Jan 13. [Epub ahead of print]

Markers of cardiovascular risk in elderly patients with age-related macular degeneration.

Mulero J1, Manresa N2, Zafrilla P1, Losada M2.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment and blindness among persons aged 60 years and older and many theories exist and feature mechanisms of oxidative stress, atherosclerotic-like changes, genetic predisposition, and inflammation in development of AMD. The aim of this study was to evaluate the association between markers of inflammation and

cardiovascular risk with age-related macular degeneration.

METHODS: Case-control study that includes 163 patients with wet AMD (age group of 55-82 years with the mean age of 71 years and 170 age-matched healthy controls in the age group of 55-78 years with the mean age of 71 years. The following parameters were determined: lipidic profile (Total Cholesterol, Triglycerides, HDL-c, LDL-c), CRP (C-Reactive Protein), homocysteine and fibrinogen.

RESULTS: We found significant differences between AMD patients and control group in baseline values of homocysteine, CRP and fibrinogen, although we do not observed differences in levels of lipidic profile.

CONCLUSION: Our data support the role of chronic inflammation in the development of AMD, however, further studies are needed to determine which common disease mechanisms of chronic inflammation and atherosclerosis contribute to the pathogenesis of AMD.

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Genetics

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Translating the ENCyclopedia Of DNA Elements Project findings to the clinic: ENCODE's implications for eye disease.

Sanfilippo PG, Hewitt AW.

Abstract: Approximately 10 years after the Human Genome Project unravelled the sequence of our DNA, the ENCyclopedia Of DNA Elements (ENCODE) Project sought to interpret it. Data from the recently completed project have shed new light on the proportion of biologically active human DNA, assigning a biochemical role to much of the sequence previously considered to be 'junk'. Many of these newly catalogued functional elements represent epigenetic mechanisms involved in regulation of gene expression. Analogous to an Ishihara plate, a gene-coding region of DNA (target dots) only comes into context when the non-coding DNA (surrounding dots) is appreciated. In this review we provide an overview of the ENCODE project, discussing the significance of these data for ophthalmic research and eye disease. The novel insights afforded by the ENCODE project will in time allow for the development of new therapeutic strategies in the management of common blinding disorders.

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