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Drug treatment

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Outcomes in Cochrane systematic reviews addressing four common eye conditions: an evaluation of completeness and comparability.

Saldanha I, Dickersin K, Wang X, Li T.

INTRODUCTION: Choice of outcomes is critical for clinical trialists and systematic reviewers. It is currently unclear how systematic reviewers choose and pre-specify outcomes for systematic reviews. Our objective was to assess the completeness of pre-specification and comparability of outcomes in all Cochrane reviews addressing four common eye conditions.

METHODS: We examined protocols for all Cochrane reviews as of June 2013 that addressed glaucoma, cataract, age-related macular degeneration (AMD), and diabetic retinopathy (DR). We assessed completeness and comparability for each outcome that was named in ≥25% of protocols on those topics. We defined a completely-specified outcome as including information about five elements: domain, specific measurement, specific metric, method of aggregation, and time-points. For each domain, we assessed comparability in how individual elements were specified across protocols.

RESULTS: We identified 57 protocols addressing glaucoma (22), cataract (16), AMD (15), and DR (4). We assessed completeness and comparability for five outcome domains: quality-of-life, visual acuity, intraocular pressure, disease progression, and contrast sensitivity. Overall, these five outcome domains appeared 145 times (instances). Only 15/145 instances (10.3%) were completely specified (all five elements) (median=three elements per outcome). Primary outcomes were more completely specified than non-primary (median=four versus two elements). Quality-of-life was least completely specified (median= one element). Due to largely incomplete outcome pre-specification, conclusive assessment of comparability in outcome usage across the various protocols per condition was not possible.

DISCUSSION: Outcome pre-specification was largely incomplete; we encourage systematic reviewers to consider all five elements. This will indicate the importance of complete specification to clinical trialists, on whose work systematic reviewers depend, and will indirectly encourage comparable outcome choice to reviewers undertaking related research questions. Complete pre-specification could improve efficiency and reduce bias in data abstraction and analysis during a systematic review. Ultimately, more completely specified and comparable outcomes could make systematic reviews more useful to decision-makers.

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Cochrane Database Syst Rev. 2014 Oct 24;10:CD007419. [Epub ahead of print]

Anti-vascular endothelial growth factor for diabetic macular oedema.

Virgili G, Parravano M, Menchini F, Evans JR.

BACKGROUND:Diabetic macular oedema (DMO) is a common complication of diabetic retinopathy. Although grid or focal laser photocoagulation has been shown to reduce the risk of visual loss in DMO, or clinically significant macular oedema (CSMO), vision is rarely improved. Antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) modalities is used to try to improve vision in people with DMO.

OBJECTIVES:To investigate the effects in preserving and improving vision and acceptability, including the safety, compliance with therapy and quality of life, of antiangiogenic therapy with anti-VEGF modalities for the treatment of DMO.

SEARCH METHODS:We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to April 2014), EMBASE (January 1980 to April 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to April 2014), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (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 28 April 2014.

SELECTION CRITERIA:We included randomised controlled trials (RCTs) comparing any antiangiogenic drugs with an anti-VEGF mechanism of action versus another treatment, sham treatment or no treatment in people with DMO.

DATA COLLECTION AND ANALYSIS:We used standard methodological procedures expected by The Cochrane Collaboration. The risk ratios (RR) for visual loss and visual gain of three or more lines of logMAR visual acuity were estimated at one year of follow-up (plus or minus six months) after treatment initiation.

MAIN RESULTS:Eighteen studies provided data on four comparisons of interest in this review. Participants in the trials had central DMO and moderate vision loss.Compared with grid laser photocoagulation, people treated with antiangiogenic therapy were more likely to gain 3 or more lines of vision at one year (RR 3.6, 95% confidence interval (CI) 2.7 to 4.8, 10 studies, 1333 cases, high quality evidence) and less likely to lose 3 or more lines of vision (RR 0.11, 95% CI 0.05 to 0.24, 7 studies, 1086 cases, high quality evidence). In meta-analyses, no significant subgroup difference was demonstrated between bevacizumab, ranibizumab and aflibercept for the two primary outcomes, but there was little power to detect a difference. The quality of the evidence was judged to be high, because the effect was large, precisely measured and did not vary across studies, although some studies were at high or unclear risk of bias for one or more domains. Regarding absolute benefit, we estimated that 8 out of 100 participants with DMO may gain 3 or more lines of visual acuity using photocoagulation whereas 28 would do so with antiangiogenic therapy, meaning that 100 participants need to be treated with antiangiogenic therapy to allow 20 more people (95% CI 13 to 29) to markedly improve their vision after one year. People treated with anti-VEGF on average had 1.6 lines better vision (95% CI 1.4 to 1.8) after one year compared to laser photocoagulation (9 studies, 1292 cases, high quality evidence). To achieve this result, seven to nine injections were delivered in the first year and three or four in the second, in larger studies adopting either as needed regimens with monthly monitoring or fixed regimens.In other analyses antiangiogenic therapy was more effective than sham (3 studies on 497 analysed participants, high quality evidence) and ranibizumab associated with laser was more effective than laser alone (4 studies on 919 participants, high quality evidence).Ocular severe adverse events, such as endophthalmitis, were rare in the included studies. Meta-analyses conducted for all antiangiogenic drugs compared with either sham or photocoagulation did not show a significant difference regarding serious systemic adverse events (15 studies, 441 events in 2985 participants, RR 0.98, 95% CI 0.83 to 1.17), arterial thromboembolic events (14 studies, 129 events in 3034 participants, RR 0.89, 95% CI

0.63 to 1.25) and overall mortality (63 events in 3562 participants, RR 0.88, 95% CI 0.52 to 1.47). We judged the quality of the evidence on adverse effects as moderate due to partial reporting of safety data and the exclusion of participants with previous cardiovascular events in some studies.

AUTHORS' CONCLUSIONS:There is high quality evidence that antiangiogenic drugs provide a benefit compared to current therapeutic options for DMO, that is grid laser photocoagulation, in clinical trial populations at one or two years. Future research should investigate differences between drugs, effectiveness under real-world monitoring and treatment conditions, and safety in high-risk populations, particularly regarding cardiovascular risk.

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PLoS One. 2014 Oct 16;9(10):e109744.

Systemic Adverse Events after Intravitreal Bevacizumab versus Ranibizumab for Age-Related Macular Degeneration: A Meta-Analysis.

Wang W, Zhang X.

OBJECTIVE: To assess whether the incidence of systemic adverse events differs between those who used bevacizumab and those who used ranibizumab in the treatment of age-related macular degeneration (AMD).

METHODS: A systematic literature search was conducted to identify randomised controlled trials (RCTs) comparing the use of intravitreal bevacizumab with the use of ranibizumab in AMD patients. Results were expressed as risk ratios (RRs) with accompanying 95% confidence intervals (CIs). The data were pooled using the fixed-effect or random-effect model according to the heterogeneity present.

RESULTS: Four RCTs were included in the final meta-analysis. Overall, the quality of the evidence was high. There were 2,613 treated patients: 1,291 treated with bevacizumab and 1,322 treated with ranibicizumab. No significant differences between bevacizumab use and ranizumab use were found in terms of the incidence of death from all causes, arteriothrombotic events, stroke, nonfatal myocardial infarction, vascular death, venous thrombotic events, and hypertension, with the pooled RRs being 1.11 (0.77, 1.61), 1.03 (0.69,1.55), 0.84 (0.39,1.80), 0.97 (0.48, 1.96), 1.24 (0.63, 2.44), 2.38 (0.94, 6.04), and 1.02 (0.29, 3.62), respectively.

CONCLUSIONS: The meta-analysis shows that both treatments are comparably safe. However, the findings from our study must be confirmed in future research via well-designed cohort or intervention studies because of the limited number of studies.

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Other treatment & diagnosis

Curr Opin Ophthalmol. 2014 Oct 18. [Epub ahead of print]

Perioperative retina evaluation of the cataract surgery patient.

Ali Khan M, Skidmore K, Ho AC.

PURPOSE OF REVIEW: To describe recent evidence regarding cataract surgery in patients with coexisting retinal disease, focusing on factors that are important to the perioperative evaluation and treatment of this patient population.

RECENT FINDINGS: Studies in patients with age-related macular degeneration have yielded good visual gains without progression of neovascular disease or increased need for intravitreal antivascular endothelial

growth factor therapy. Uveitic patients similarly gain vision on average, and control of inflammation remains paramount. Perioperative treatment with intravitreal antivascular endothelial growth factor and corticosteroid help mitigate postoperative macular edema in patients with diabetic macular edema. Risk of retinal detachment is elevated postcataract surgery, but evidence regarding prophylactic treatment of peripheral retinal pathology is lacking. Intracameral antibiotics have reduced rates of postcataract surgery endophthalmitis in recent population-based retrospective studies.

SUMMARY: Favorable visual acuity outcomes are possible following cataract surgery in patients with retinal disease, including uveitis, diabetic macular edema, and age-related macular degeneration. Perioperative control of retinal disease activity is desired, but level 1 evidence to guide best practices regarding optimal timing and nature of perioperative treatment remains limited. Prevention of postoperative retinal detachment and endophthalmitis is deserving of additional study.

PMID: 25333755 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2014 Oct 21. [Epub ahead of print]

Assessment of laser induction of Bruch's membrane disruption in monkey by spectral-domain optical coherence tomography.

Wang Q, Lin X, Xiang W, Xiao W, He M.

PURPOSE: Laser-induced choroidal neovascularisation is a widely used model for age-related macular degeneration. The success rates of induction have been relatively low in large animals such as monkeys. Our study aimed to investigate the laser-induced damages to the Bruch's membrane of monkeys using the spectral-domain optical coherence tomography (OCT).

METHODS: Laser photocoagulation was performed in the posterior and peripheral fundus of a rhesus monkey using a 532 nm laser. The lesions were examined by fundus photography and spectral-domain OCT immediately after the procedure. Fluorescein angiography was performed after 3 and 4 weeks in the animal to assess the development of choroidal neovascularisation.

RESULTS: A total of 44 lesions were produced in both eyes of the animal. Subretinal bubbles with or without haemorrhage were observed at 41 spots during the procedure. Spectral-domain OCT showed that laser damages varied considerably among lesions and the disruption of the Bruch's membrane could be visualised at 23 spots on the OCT images. Leakage of fluorescein was only observed after 3 and 4 weeks within the macular area at lesions where Bruch's membrane disruptions had been detected by OCT.

CONCLUSIONS: The presence of subretinal bubbles with haemorrhage is not an accurate indicator for successful disruption of the Bruch's membrane. Instead, spectral-domain OCT provides a better alternative to assess the retinal damages to the Bruch's membrane during laser induction of choroidal neovascularisation in monkeys.

PMID: 25336578 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2014 Nov;92(7):709.

Development of gene therapy for treatment of age-related macular degeneration.

Askou AL.

PMID: 25328993 [PubMed - in process]

Pathogenesis

PLoS One. 2014 Oct 24;9(10):e111472.

Lack of Involvement of CEP Adducts in TLR Activation and in Angiogenesis.

Gounarides J, Cobb JS, Zhou J et al

Abstract: Proteins that are post-translationally adducted with 2-(ω-carboxyethyl)pyrrole (CEP) have been proposed to play a pathogenic role in age-related macular degeneration, by inducing angiogenesis in a Toll Like Receptor 2 (TLR2)-dependent manner. We have investigated the involvement of CEP adducts in angiogenesis and TLR activation, to assess the therapeutic potential of inhibiting CEP adducts and TLR2 for ocular angiogenesis. As tool reagents, several CEP-adducted proteins and peptides were synthetically generated by published methodology and adduction was confirmed by NMR and LC-MS/MS analyses. Structural studies showed significant changes in secondary structure in CEP-adducted proteins but not the untreated proteins. Similar structural changes were also observed in the treated unadducted proteins, which were treated by the same adduction method except for one critical step required to form the CEP group. Thus some structural changes were unrelated to CEP groups and were artificially induced by the synthesis method. In biological studies, the CEP-adducted proteins and peptides failed to activate TLR2 in cell-based assays and in an in vivo TLR2-mediated retinal leukocyte infiltration model. Neither CEP adducts nor TLR agonists were able to induce angiogenesis in a tube formation assay. In vivo, treatment of animals with CEP-adducted protein had no effect on laser-induced choroidal neovascularization. Furthermore, in vivo inactivation of TLR2 by deficiency in Myeloid Differentiation factor 88 (Myd88) had no effect on abrasion-induced corneal neovascularization. Thus the CEP-TLR2 axis, which is implicated in other wound angiogenesis models, does not appear to play a pathological role in a corneal wound angiogenesis model. Collectively, our data do not support the mechanism of action of CEP adducts in TLR2-mediated angiogenesis proposed by others.

PMID: 25343517 [PubMed - as supplied by publisher]

Toxicol Sci. 2014 Oct 20. [Epub ahead of print]

Involvement of Endoplasmic Reticulum Stress in All-trans-retinal Induced Retinal Pigment Epithelium Degeneration.

Li J, Cai X, Xia Q, Yao K, Chen J, Zhang Y, Naranmandura H, Liu X, Wu Y.

Abstract: Excess accumulation of endogenous all-trans-retinal (atRAL) contributes to degeneration of the retinal pigment epithelium (RPE) and photoreceptor cells, and plays a role in the etiologies of age-related macular degeneration (AMD) and Stargardt's disease. In this study, we reveal that human RPE cells tolerate exposure of up to 5 μM atRAL without deleterious effects, but higher concentrations are detrimental and induce cell apoptosis. atRAL treatment significantly increased production of intracellular reactive oxygen species (ROS) and up-regulated mRNA expression of Nrf2, HO-1, and γ-GCSh within RPE cells, thereby causing oxidative stress. ROS localized to mitochondria and endoplasmic reticulum (ER). ER resident molecular chaperone BiP, a marker of ER stress, was up-regulated at the translational level, and meanwhile, the PERK-eIF2α-ATF4 signaling pathway was activated. Expression levels of ATF4, CHOP, and GADD34 in RPE cells increased in a concentration-dependent manner after incubation with atRAL. Salubrinal, a selective inhibitor of ER stress, alleviated atRAL-induced cell death. The antioxidant N-acetylcysteine (NAC) effectively blocked RPE cell loss and ER stress activation, suggesting that atRAL-induced ROS generation is responsible for RPE degeneration and is an early trigger of ER stress. Furthermore, the mitochondrial transmembrane potential was lost after atRAL exposure, and was followed by caspase-3 activation and PARP cleavage. The results demonstrate that atRAL-driven ROS overproduction induced ER stress is involved in cellular mitochondrial dysfunction and apoptosis of RPE cells.

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Epidemiology

JAMA Ophthalmol. 2014 Oct 23. [Epub ahead of print]

Severity of Age-Related Macular Degeneration in 1 Eye and the Incidence and Progression of Age-Related Macular Degeneration in the Fellow Eye: The Beaver Dam Eye Study.

Gangnon RE, Lee KE, Klein BE, Iyengar SK, Sivakumaran TA, Klein R.

Importance: Previous studies regarding the severity of age-related macular degeneration (AMD) in 1 eye and its prognostic implications for the fellow eye have focused on the incidence of neovascular AMD in the fellow eye of participants with neovascular AMD in the other eye. It is unclear to what extent the severity of AMD in 1 eye affects the incidence, progression, and regression of AMD in its fellow eye across the entire range of AMD severity.

Objective: To investigate the effect of the severity of AMD in 1 eye on the incidence, progression, and regression of AMD in the fellow eye.

Design, Setting and Participants: The Beaver Dam Eye Study is a longitudinal population-based study of age-related eye diseases conducted in the city and township of Beaver Dam, Wisconsin. Examinations were performed every 5 years over a 20-year period (from the baseline examination in 1988-1990 to 2008-2010). Study participants (n = 4379) were 43 to 86 years of age at the baseline examination. At baseline and in up to 4 subsequent examinations, retinal photographs were taken.

Main Outcomes and Measures: Incidence, progression, and regression of AMD (assessed by use of the Wisconsin Age-Related Maculopathy Grading System on retinal photographs and adjusted for age, sex, and the Y402H polymorphism in the complement factor H gene on chromosome 1q) and mortality.

Results: More severe AMD in 1 eye was associated with increased incidence of AMD and accelerated progression in its fellow eye (levels 1-2: hazard ratio [HR], 4.90 [95% CI, 4.26-5.63]; levels 2-3: HR, 2.09 [95% CI, 1.42-3.06]; levels 3-4: HR, 2.38 [95% CI, 1.74-3.25]; levels 4-5: HR, 2.46 [95% CI, 1.65-3.66]). Less severe AMD in 1 eye was associated with less progression of AMD in its fellow eye (levels 2-3: HR, 0.42 [95% CI, 0.33-0.55]; levels 3-4: HR, 0.50 [95% CI, 0.34-0.83]). We estimate that 51% of participants who develop any AMD always maintain AMD severity states within 1 step of each other between eyes; 90% of participants stay within 2 steps.

Conclusions and Relevance: Using multistate models, we show that AMD severity in 1 eye tracks AMD severity in its fellow eye.

PMID: 25340497 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Oct 21. pii: IOVS-14-14471. doi: 10.1167/iovs.14-14471. [Epub ahead of print]

Lifetime exposure to ambient ultraviolet radiation and the risk for cataract extraction and age-related macular degeneration: the Alienor Study.

Delcourt C, Cougnard-Grégroire A, Boniol M, Carrière I, Doré JF, Delyfer MN, Rougier MB, Le Goff M, Dartigues JF, Barberger-Gateau P, Korobelnik JF.

Purpose: While exposure to ultraviolet radiation is a recognized risk factor for cataract, its association is more controversial with age-related macular degeneration (AMD). We report the associations of lifetime exposure to ambient ultraviolet radiation (UVR) with cataract extraction and AMD.

Methods: The Alienor Study is a population-based study of 963 residents of Bordeaux (France), aged 73 years or more. Lifetime exposure to ambient UVR was estimated from residential history and Eurosun

satellite-based estimations of ground UVR. It was divided in 3 groups (lower quartile, intermediate quartiles, upper quartile), using the intermediate quartiles as the reference. Early and late AMD were classified from retinal colour photographs. Cataract extraction was defined as absence of the natural lens at slit lamp.

Results: After multivariate adjustment, subjects in the upper quartile of lifetime ambient UVR exposure were at increased risk for cataract extraction (OR=1.53, 95 % confidence interval (CI): 1.04-2.26, p=0.03) and for early AMD (OR= 1.59, 95 % CI: 1.04-2.44, p=0.03), by comparison with subjects in the intermediate quartiles. Subjects in the lower quartile of UVR exposure were also at increased risk for early AMD (OR=1.69, 95 % CI: 1.06-2.69, p=0.03), by comparison with those with medium exposure. Associations of late AMD with UVR exposure was not statistically significant.

Conclusions: This study further confirms the increased risk for cataract extraction in subjects exposed to high ambient UVR. Moreover, it suggests that risk for early AMD is increased in subjects exposed to high UVR, but also to low UVR, by comparison with medium exposures.

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Genetics

Cold Spring Harb Perspect Med. 2014 Oct 23. [Epub ahead of print]

Differential Gene Expression in Age-Related Macular Degeneration.

Morgan DJ, DeAngelis MM.

Abstract: Gene expression is the first step in ascribing function between an associated gene and disease. Understanding how variation in a gene influences expression, particularly in tissues affected by the disease, may help elucidate what influences the phenotypic outcome of that disease. Previous studies of the genetics of age-related macular degeneration (AMD) have identified several risk factors, but have not yet bridged the gap between gene association and identifying a specific mechanism or function that is involved in the pathogenesis of AMD. Advances in genomic technologies, such as RNA sequencing (RNA-seq), single cell RNA-seq, bilsulfite sequencing, and/or whole genome methylation, will be powerful tools for identifying genes/pathways that are differentially expressed in those with AMD versus those without AMD. These technologies should advance the field of AMD research so that appropriate preventive and therapeutic targets can be developed.

PMID: 25342062 [PubMed - as supplied by publisher]

Diet & lifestyle

Clin Ophthalmol. 2014 Oct 10;8:2045-53.

European survey on the opinion and use of micronutrition in age-related macular degeneration: 10 years on from the Age-Related Eye Disease Study.

Aslam T, Delcourt C, Holz F, García-Layana A, Leys A, Silva RM, Souied E.

PURPOSE: To evaluate ophthalmologists' opinion of, and use of, micronutritional dietary supplements 10 years after publication of the first Age-Related Eye Disease Study (AREDS) study.

METHODS: Participation was solicited from 4,000 European ophthalmologists. Responding physicians were screened, and those treating at least 40 patients with age-related macular degeneration (AMD) per month and prescribing nutrition supplements at least 4 times per month were admitted and completed a 40-item questionnaire.

RESULTS: The surveyed sample included 112 general ophthalmologists and 104 retinal specialists. Most nutritional supplements (46%) were initiated when early/intermediate AMD was confirmed, although 18% were initiated on confirmation of neovascular AMD. Clinical studies were well known: 90% were aware of AREDS, with 88% aware of AREDS1 and 36% aware of the, as-yet-unpublished, AREDS2 studies. Respondents considered lutein, zeaxanthin, zinc, omega-3, and vitamins to be the most important components of nutritional supplements, with the results of AREDS2 already having been taken into consideration by many. Ophthalmologists anticipate more scientific studies as well as improved product quality but identify cost as a barrier to wider uptake.

CONCLUSION: Micronutrition is now part of the routine management of AMD for many ophthalmologists. Ophthalmologists choosing to use nutritional supplements are well-informed regarding current scientific studies.

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Nutrients. 2014 Oct 17;6(10):4404-20.

Resveratrol based oral nutritional supplement produces long-term beneficial effects on structure and visual function in human patients.

Richer S, Patel S, Sockanathan S, Ulanski LJ, Miller L, Podella C.

BACKGROUND: Longevinex® (L/RV) is a low dose hormetic over-the-counter (OTC) oral resveratrol (RV) based matrix of red wine solids, vitamin D3 and inositol hexaphosphate (IP6) with established bioavailability, safety, and short-term efficacy against the earliest signs of human atherosclerosis, murine cardiac reperfusion injury, clinical retinal neovascularization, and stem cell survival. We previously reported our short-term findings for dry and wet age-related macular degeneration (AMD) patients. Today we report long term (two to three year) clinical efficacy.

METHODS: We treated three patients including a patient with an AMD treatment resistant variant (polypoidal retinal vasculature disease). We evaluated two clinical measures of ocular structure (fundus autofluorescent imaging and spectral domain optical coherence extended depth choroidal imaging) and qualitatively appraised changes in macular pigment volume. We further evaluated three clinical measures of visual function (Snellen visual acuity, contrast sensitivity, and glare recovery to a cone photo-stress stimulus).

RESULTS: We observed broad bilateral improvements in ocular structure and function over a long time period, opposite to what might be expected due to aging and the natural progression of the patient's pathophysiology. No side effects were observed.

CONCLUSIONS: These three cases demonstrate that application of epigenetics has long-term efficacy against AMD retinal disease, when the retinal specialist has exhausted other therapeutic modalities.

PMID: 25329968 [PubMed - in process]

Int J Mol Sci. 2014 Oct 17;15(10):18762-75.

Squamosamide Derivative FLZ Protects Retinal Pigment Epithelium Cells from Oxidative Stress through Activation of Epidermal Growth Factor Receptor (EGFR)-AKT Signaling.

Cheng LB, Chen CM, Zhong H, Zhu LJ.

Abstract: Reactive oxygen species (ROS)-mediated retinal pigment epithelium (RPE) cell apoptosis is attributed to age-related macular degeneration (AMD) pathogenesis. FLZ, a novel synthetic squamosamide derivative from a Chinese herb, Annona glabra, has displayed significant cyto-protective activity. In the

current study, we explored the pro-survival effect of FLZ in oxidative stressed-RPE cells and studied the underlying signaling mechanisms. Our results showed that FLZ attenuated hydrogen peroxide (H2O2)-induced viability decrease and apoptosis in the RPE cell line (ARPE-19 cells) and in primary mouse RPE cells. Western blotting results showed that FLZ activated AKT signaling in RPE cells. The AKT-specific inhibitor, MK-2206, the phosphoinositide 3-kinase (PI3K)/AKT pan inhibitor, wortmannin, and AKT1-shRNA (short hairpin RNA) depletion almost abolished FLZ-mediated pro-survival/anti-apoptosis activity. We discovered that epidermal growth factor receptor (EGFR) trans-activation mediated FLZ-induced AKT activation and the pro-survival effect in RPE cells, and the anti-apoptosis effect of FLZ against H2O2 was inhibited by the EGFR inhibitor, PD153035, or by EGFR shRNA-knockdown. In conclusion, FLZ protects RPE cells from oxidative stress through activation of EGFR-AKT signaling, and our results suggest that FLZ might have therapeutic values for AMD.

PMID: 25329617 [PubMed - in process]