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MD Research News

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Drug treatment

Ophthalmology. 2014 Mar 26. pii: S0161-6420(14)00071-2. doi: 10.1016/j.ophtha.2014.01.027. [Epub ahead of print]

Intravitreal Aflibercept Injection for Macular Edema Due to Central Retinal Vein Occlusion: Two-Year Results from the COPERNICUS Study.

Heier JS, Clark WL, Boyer DS, Brown DM, Vitti R, Berliner AJ, Kazmi H, Ma Y, Stemper B, Zeitz O, Sandbrink R, Haller JA.

PURPOSE: To evaluate the efficacy and safety of intravitreal aflibercept injection (IAI) for the treatment of macular edema secondary to central retinal vein occlusion (CRVO).

DESIGN: Randomized, double-masked, phase 3 trial.

PARTICIPANTS: A total of 188 patients with macular edema secondary to CRVO.

METHODS: Patients received IAI 2 mg (IAI 2Q4) (n = 114) or sham injections (n = 74) every 4 weeks up to week 24. During weeks 24 to 52, patients from both arms were evaluated monthly and received IAI as needed, or pro re nata (PRN) (IAI 2Q4 + PRN and sham + IAI PRN). During weeks 52 to 100, patients were evaluated at least quarterly and received IAI PRN.

MAIN OUTCOME MEASURES: The primary efficacy end point was the proportion of patients who gained ≥15 letters in best-corrected visual acuity (BCVA) from baseline to week 24. This study reports week 100 results.

RESULTS: The proportion of patients gaining ≥15 letters was 56.1% versus 12.3% (P<0.001) at week 24, 55.3% versus 30.1% (P<0.001) at week 52, and 49.1% versus 23.3% (P<0.001) at week 100 in the IAI 2Q4 + PRN and sham + IAI PRN groups, respectively. The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + PRN group compared with the sham + IAI PRN group at week 24 (+17.3 vs. -4.0 letters; P<0.001), week 52 (+16.2 vs. +3.8 letters; P<0.001), and week 100 (+13.0 vs. +1.5 letters; P<0.0001). The mean reduction from baseline in central retinal thickness was 457.2 versus 144.8 μm (P<0.001) at week 24, 413.0 versus 381.8 μm at week 52 (P = 0.546), and 390.0 versus 343.3 μm at week 100 (P = 0.366) in the IAI 2Q4 + PRN and sham + IAI PRN groups, respectively. The mean number (standard deviation) of PRN injections in the IAI 2Q4 + PRN and sham + IAI PRN groups was 2.7±1.7 versus 3.9±2.0 during weeks 24 to 52 and 3.3±2.1 versus 2.9±2.0 during weeks 52 to 100, respectively. The most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (0.9% vs. 6.8% in the IAI 2Q4 + PRN and sham + IAI PRN groups, respectively).

CONCLUSIONS: The visual and anatomic improvements after fixed dosing through week 24 and PRN dosing with monthly monitoring from weeks 24 to 52 were diminished after continued PRN dosing, with a reduced monitoring frequency from weeks 52 to 100.

PMID: 24679444 [PubMed - as supplied by publisher]

Drugs Today (Barc). 2014 Mar;50(3):239-49. doi: 10.1358/dot.2014.50.3.2103755.

An update on intravitreal implants in use for eye disorders.

Lambiase A, Abdolrahimzadeh S, Recupero SM.

Abstract: Advanced biotechnological techniques and new polymers have led to the development of many innovative intravitreal drug delivery systems. Some designs are still in an experimental phase while others have gained widespread acceptance and are commercially available. Since steroids are a mainstay of therapy for uveitis and macular edema, new intravitreal implants have been developed to provide continuous release of corticosteroids over prolonged spans of time with reduced systemic adverse effects. Today, three long-acting corticosteroid implants are commercially available: the fluocinolone acetonide implants Retisert® and Iluvien® and the dexamethasone drug delivery system Ozurdex®. They offer an alternative route in the management of macular edema due to uveitis, retinal vein occlusion, diabetes and pseudophakia. Their advantage over treatment with steroid injections and the anti-vascular endothelial growth factor ranibizumab is the long-term control of inflammation and macular edema with a reduced frequency of administration. Their potential side effects are cataract and glaucoma, therefore, careful patient selection and monitoring is essential. Further studies are warranted to define the relative efficacy and indications for each treatment option. The development of new devices is a future challenge in the strive to improve drug delivery systems.

PMID: 24696869 [PubMed - in process]

Wien Klin Wochenschr. 2014 Apr 3. [Epub ahead of print]

Differences of frequency in administration of ranibizumab and bevacizumab in patients with neovascular AMD.

Scholler A, Richter-Mueksch S, Weingessel B, Vécsei-Marlovits PV.

PURPOSE: Intravitreal ranibizumab or bevacizumab are the most used drugs for treatment of neovascular age-related macular degeneration (nAMD). Repeated intravitreal injections represent an economic burden and may be associated with serious complications. The aim of this study is to evaluate the number of needed injections within 1 year of treatment.

METHODS: 55 patients over 50 years of age with nAMD and visual acuity (VA) between 20/40 and 20/320 were included. Scheduled visits and treatment were performed monthly for 1 year. After a loading dose of three intravitreal injections (either ranibizumab = group 1 or bevacizumab = group 2), an "as needed" regimen was performed. Primary endpoint was a difference in the injection frequencies of ranibizumab and bevacizumab. Secondary endpoints were best corrected visual acuity (BCVA) and central retinal thickness (CRT).

RESULTS: Difference in number of injections was not significant (5.00 ± 1.67 (ranibizumab group) vs. 5.80 ± 2.28 (bevacizumab group), p = 0.084). Mean BCVA was 59.12 ± 16.64 letters after 12 months if patients received ranibizumab (p = 0.001) and 64.75 ± 17.03 letters if patients received bevacizumab (p = 0.037). There was no statistical significance between the two groups (p = 0.631). The mean CRT did not differ significantly between groups after 12 months (315.67 ± 65.86 µm for ranibizumab, 350.47 ± 102.84 µm for bevacizumab, p = 0.088).

CONCLUSION: There was no difference in number of treatment, BCVA and CRT after 1 year between ranibizumab and bevacizumab in patients with nAMD.

PMID: 24696051 [PubMed - as supplied by publisher]

J Ophthalmol. 2014;2014:346360. doi: 10.1155/2014/346360. Epub 2014 Feb 16.

Age-Related Macular Degeneration: Clinical Findings following Treatment with Antiangiogenic Drugs.

Casaroli-Marano R, Gallego-Pinazo R, Fernández-Blanco CT, Figueroa MS, Pina Marín B, Fernández-Baca Vaca G, Piñero-Bustamante A, Donate López J, García-Arumí J, Farrés Martí J.

Purpose: To survey the management of patients with neovascular age-related macular degeneration (nvAMD) in Spain.

Methods: An observational retrospective multicenter study was conducted. The variables analyzed were sociodemographic characteristics, foveal and macular thickness, visual acuity (VA), type of treatment, number of injections, and the initial administration of a loading dose of an antiangiogenic drug.

Results: 208 patients were followed up during 23.4 months in average. During the first and second years, patients received a mean of 4.5 ± 1.8 and 1.6 ± 2.1 injections of antiangiogenic drugs, and 5.4 ± 2.8 and 3.6 ± 2.2 follow-up visits were performed, respectively. The highest improvement in VA was observed at 3 months of follow-up, followed by a decrease in the response that stabilized above baseline values until the end of the study. Patients who received an initial loading dose presented greater VA gains than those without.

Conclusions: Our results suggest the need for a more standardized approach in the management and diagnosis of nvAMD receiving VEGF inhibitors. To achieve the visual outcomes reported in pivotal trials, an early diagnosis, proactive approach (more treating than follow-up visits), and a close monitoring might be the key to successfully manage nvAMD.

PMID: 24693418 [PubMed] PMCID: PMC3945152

Ophthalmology. 2014 Mar 28. pii: S0161-6420(13)01245-1. doi: 10.1016/j.ophtha.2013.12.029. [Epub ahead of print]

Morphologic Parameters Relevant for Visual Outcome During Anti-Angiogenic Therapy of Neovascular Age-Related Macular Degeneration.

Simader C, Ritter M, Bolz M, Deák GG, Mayr-Sponer U, Golbaz I, Kundi M, Schmidt-Erfurth UM.

PURPOSE: To identify the effects of anti-angiogenic therapy in neovascular age-related macular degeneration (AMD) in respect to morphologic type and time course and to identify prognostic factors for visual outcome on the basis of standardized optical coherence tomography (OCT) analysis.

DESIGN: Subanalysis of a prospective, 12-month, multicenter, phase IIIb trial (Efficacy and Safety of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration [EXCITE]).

PARTICIPANTS: A total of 353 treatment-naïve patients with subfoveal choroidal neovascularization (CNV) receiving quarterly or monthly ranibizumab therapy.

METHODS: Patients were randomized to receive 0.3 mg quarterly, 0.5 mg quarterly, or 0.3 mg monthly doses of ranibizumab. Treatment comprised a loading phase of 3 consecutive monthly injections followed

by a 9-month maintenance phase of monthly or quarterly injections. Best-corrected visual acuity (BCVA) was measured using the Early Treatment Diabetic Retinopathy Study protocol, and retinal morphology was assessed by Stratus OCT (Carl Zeiss Meditec, Dublin, CA). Imaging data were evaluated by certified examiners of the Vienna Reading Center using a standardized protocol.

MAIN OUTCOME MEASURES: The BCVA was measured using ETDRS charts and retinal morphology was assessed by OCT.

RESULTS: During the loading phase, there was a significant correlation between a reduction in central retinal thickness and an increase in BCVA ($P < 0.001$), which decreased during the maintenance phase in all treatment arms. The proportion of patients showing retinal morphologic changes, such as intraretinal cysts (IRCs), subretinal fluid (SRF), and pigment epithelial detachments (PEDs), decreased significantly in all groups ($P < 0.001$), more intensively in the 0.5 mg quarterly than in both 0.3 mg groups. Intraretinal cysts resolved most rapidly followed by SRF, whereas PED decreased at a slower rate and intensity. Patients with IRC at baseline had lower BCVA levels that remained lower over the entire study period, whereas recurrence of IRC during follow-up showed no additional negative effect on function. Baseline SRF had no effect on visual recovery; however, recurrence of SRF during follow-up showed a tendency for an additional negative effect on function ($P = 0.06$). Baseline PED showed a negative influence on visual outcome only in combination with IRC and SRF.

CONCLUSIONS: There is a distinct response pattern and time course of morphologic parameters associated with anti-vascular endothelial growth factor therapy in neovascular AMD. Specific alterations, such as IRC, SRF, and PED, as baseline or follow-up features are significantly influencing the potential for visual gain.

PMID: 24684838 [PubMed - as supplied by publisher]

Ocul Immunol Inflamm. 2014 Mar 28. [Epub ahead of print]

Intravitreal Ranibizumab for the Treatment of Irvine-Gass Syndrome.

Mitropoulos PG, Chatziralli IP, Peponis VG, Drakos E, Parikakis EA.

Abstract Purpose: The purpose of our study was to evaluate the potential efficacy and safety of intravitreal ranibizumab in patients with pseudophakic cystoid macular edema (CME).

Methods: This retrospective study comprised 7 eyes with CME treated with intravitreal ranibizumab. Patients were examined at 1 week and 1 month after injection and monthly thereafter. Main outcome measures included changes in best-corrected visual acuity (BCVA) and central retinal thickness (CRT). Safety was assessed by ophthalmic examination and report of systemic adverse effects.

Results: There was a statistically significant difference on BCVA ($p < 0.001$) and CRT ($p < 0.001$) before and after the ranibizumab injection. One injection appeared to be sufficient for the resolution of CME, while recurrence was observed in 1 patient, in a long-term follow-up. No observable ocular or systemic side effects were found.

Conclusions: Intravitreal ranibizumab seems to be effective and safe for the treatment of pseudophakic CME, demonstrating a statistically significant difference in BCVA as well as CRT.

PMID: 24678790 [PubMed - as supplied by publisher]

Vestn Oftalmol. 2014 Jan-Feb;130(1):37-41.

[Morphometric assessment of the macula in spongiform macular edema treated with antivasoproliferative therapy].[Article in Russian]

[No authors listed]

Abstract: Antivasoproliferative therapy is a pathogenetic treatment for diabetic macular edema. The objective of the study was to investigate the effect of ranibizumab on foveolar parameters in spongiform macular edema. A total of 37 patients (38 eyes) with spongiform macular edema were assessed and given antivasoproliferative therapy with ranibizumab. Optical coherence tomography showed a reduction of the total retinal thickness by 44 microm (from 306 +/- 77 microm to 262 +/- 30 microm, $p < 0.05$). The pigment epithelium thickness within the central area changed from 21 +/- 4 microm to 40 +/- 9 microm. The maximum decrease of the outer nuclear layer thickness was noted in 400 +/- 100 microm from foveola and averaged from 72 +/- 19 microm to 29 +/- 6 microm with its gradual increase to the periphery to 100 +/- 8 microm.

PMID: 24684064 [PubMed - in process]

Vestn Oftalmol. 2014 Jan-Feb;130(1):12-7.

[Morphological characteristics of the macula in patients with retinal vein occlusion before and after the treatment: preliminary results].[Article in Russian]

[No authors listed]

Abstract: The article presents examination results of 26 patients with macular edema (ME) due to retinal vein occlusion (RVO) before and 1 month after an intravitreal injection of ranibizumab (Lucentis). Besides routine assessment, retinal spectral-domain optical coherent tomography (OCT) was performed in all cases. In accordance with derived OCT patterns of macular edema the patients were devided into two groups: swelling of the inner and outer retinal layers with serous detachment of neuroepithelium (group 1) and intraretinal edema with pseudocysts (group 2). It is shown that initial OCT features of retina in patients with ME due to RVO are prognostic for treatment results (serous retinal detachment may serve as a preventing factor of photoreceptor damage) and that visual improvement in patients with ME and serous detachment of neuroepithelium anticipates morphological changes.

PMID: 24684060 [PubMed - in process]

J Clin Invest. 2014 Apr 1;124(4):1430-8. doi: 10.1172/JCI71029. Epub 2014 Apr 1.

Recent developments in the treatment of age-related macular degeneration.

Holz FG, Schmitz-Valckenberg S, Fleckenstein M.

Abstract: Age-related macular degeneration (AMD) is a common cause of visual loss in the elderly, with increasing prevalence due to increasing life expectancy. While the introduction of anti-VEGF therapy has improved outcomes, there are still major unmet needs and gaps in the understanding of underlying biological processes. These include early, intermediate, and atrophic disease stages. Recent studies have assessed therapeutic approaches addressing various disease-associated pathways, including complement inhibitors. Drug-delivery aspects are also relevant, as many agents have to be administered repeatedly. Herein, relevant pathogenetic factors and underlying mechanisms as well as recent and potential therapeutic approaches are reviewed.

PMID: 24691477 [PubMed - in process] PMCID: PMC3973093

Other treatment & diagnosis

Retina. 2014 Apr 1. [Epub ahead of print]

SUBRETINAL HYPERREFLECTIVE EXUDATION ASSOCIATED WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Shah VP, Shah SA, Mrejen S, Freund KB.

PURPOSE: To describe the multimodal imaging findings of subretinal hyperreflective exudation (SHE) observed in association with choroidal neovascularization and to distinguish SHE from other forms of subretinal hyperreflective material (SHM) seen in patients with age-related macular degeneration and other macular disorders.

METHODS: A retrospective study on 46 eyes of 42 patients with SHE associated with Types 1, 2, and 3 choroidal neovascularization secondary to neovascular age-related macular degeneration. Patients were examined using multimodal imaging, including color photography, near-infrared reflectance imaging, spectral domain optical coherence tomography, fluorescein angiography, fundus autofluorescence imaging, and indocyanine green angiography. Clinical and imaging characteristics were evaluated at baseline, after the initiation of intravitreal antivascular endothelial growth factor therapy, and during the resolution of SHE.

RESULTS: Forty-five of the 46 eyes were treatment naive. The mean ± SD age at the first detection of SHE was 77.2 ± 10.1 years. The mean ± SD follow-up was 2.1 ± 0.6 years. Fluorescein angiography was performed in 42 eyes and demonstrated leakage and/or staining of underlying or adjacent choroidal neovascularization but not of the SHE itself in all eyes. On fluorescein angiography, SHE was transparent in 29 eyes and blocking in 7 eyes. In 32 eyes, SHE showed isoautofluorescence on fundus autofluorescence imaging, and in 8 eyes, SHE showed varying degrees of hyperautofluorescence. Indocyanine green angiography was performed in eight eyes and demonstrated hyperfluorescence of SHE in seven eyes. In eight eyes, SHE was the only evidence of neovascular activity. All eyes having follow-up (42 eyes) showed resolution of the subretinal material with partial or full reconstitution of the ellipsoid zone after a median of 2 injections range (1-16 injections). Subretinal hyperreflective exudation persisted for a median of 9 weeks (range, 4-60 weeks) after the initiation of treatment. The mean visual acuity before treatment was 0.619 (20/83), and it improved to 0.380 (20/48) (P = 0.03) after the resolution of SHE.

CONCLUSION: Subretinal hyperreflective exudation differs from other types of SHM based on the findings from multimodal imaging. This novel type of SHM likely represents a sign of active neovascular age-related macular degeneration distinct from subretinal fluid, hemorrhage, neovascular tissue, lipid, pigment hyperplasia, subretinal fibrosis, and the SHM observed with acquired vitelliform lesions. Intravitreal antivascular endothelial growth factor agents can be used to successfully resolve SHE, often resulting in better visual outcomes in eyes manifesting this form of exudation.

PMID: 24695062 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Mar 26. pii: S0161-6420(14)00104-3. doi: 10.1016/j.ophtha.2014.01.034. [Epub ahead of print]

Quantitative Optical Coherence Tomography Angiography of Choroidal Neovascularization in Age-related Macular Degeneration.

Jia Y, Bailey ST, Wilson DJ, Tan O, Klein ML, Flaxel CJ, Potsaid B, Liu JJ, Lu CD, Kraus MF, Fujimoto JG, Huang D.

PURPOSE: To detect and quantify choroidal neovascularization (CNV) in patients with age-related macular degeneration (AMD) using optical coherence tomography (OCT) angiography.

DESIGN: Observational, cross-sectional study.

PARTICIPANTS: A total of 5 normal subjects and 5 subjects with neovascular AMD were included.

METHODS: A total of 5 eyes with neovascular AMD and 5 normal age-matched controls were scanned by a high-speed (100 000 A-scans/seconds) 1050-nm wavelength swept-source OCT. The macular angiography scan covered a 3×3-mm area and comprised 200×200×8 A-scans acquired in 3.5 seconds. Flow was detected using the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm. Motion artifacts were removed by 3-dimensional (3D) orthogonal registration and merging of 4 scans. The 3D angiography was segmented into 3 layers: inner retina (to show retinal vasculature), outer retina (to identify CNV), and choroid. En face maximum projection was used to obtain 2-dimensional angiograms from the 3 layers. The CNV area and flow index were computed from the en face OCT angiogram of the outer retinal layer. Flow (decorrelation) and structural data were combined in composite color angiograms for both en face and cross-sectional views.

MAIN OUTCOME MEASUREMENTS: The CNV angiogram, CNV area, and CNV flow index.

RESULTS: En face OCT angiograms of CNV showed sizes and locations that were confirmed by fluorescein angiography (FA). Optical coherence tomography angiography provided more distinct vascular network patterns that were less obscured by subretinal hemorrhage. The en face angiograms also showed areas of reduced choroidal flow adjacent to the CNV in all cases and significantly reduced retinal flow in 1 case. Cross-sectional angiograms were used to visualize CNV location relative to the retinal pigment epithelium and Bruch's layer and classify type I and type II CNV. A feeder vessel could be identified in 1 case. Higher flow indexes were associated with larger CNV and type II CNV.

CONCLUSIONS: Optical coherence tomography angiography provides depth-resolved information and detailed images of CNV in neovascular AMD. Quantitative information regarding CNV flow and area can be obtained. Further studies are needed to assess the role of quantitative OCT angiography in the evaluation and treatment of neovascular AMD.

PMID: 24679442 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Apr 3. pii: iovs.13-13409v1. doi: 10.1167/iovs.13-13409. [Epub ahead of print]

The "Diffuse-Trickling" Fundus Autofluorescence Phenotype in Geographic Atrophy.

Fleckenstein M, Schmitz-Valckenberg S, Lindner M, Bezatis A, Becker E, Fimmers R, Holz FG.

Purpose: To further characterize a subgroup of patients exhibiting the fundus autofluorescence (FAF) "diffuse-trickling" phenotype associated with geographic atrophy (GA).

Methods: In the context of the Fundus Autofluorescence in Age related Macular Degeneration (FAM) Study, patients with "diffuse-trickling" GA were examined and characterized by FAF and spectral-domain optical coherence tomography imaging (HRA, Spectralis HRA+OCT, Heidelberg Engineering). Age, gender distribution, and medical history were compared to FAM study patients (n=288, 60.1% female) with other GA phenotypes ("non-diffuse-trickling"). In a subset of patients, subfoveal choroidal thickness (SCT) was analyzed.

Results: Patients with "diffuse-trickling" (n=61) - compared to patients with "non-diffuse-trickling" GA - had a significantly younger age at first presentation (68.2±11.6 vs.75.4±8.1 years, p<0.001), a shift in the proportion of men from 55% in the age group <65 to 19% in the age group ≥65, and a significantly higher rate of myocardial infarction (MI) in the age group <65 (24% vs. 0%,p=0.011); all but one patient with MI were male. Further evaluation revealed that in the age group <65, 54% of patients with "diffuse-trickling" had been hospitalized due to cardiovascular diseases including hypertensive crisis, angina, and MI. Analysis of choroidal thickness revealed a significantly thinner SCT in "diffuse-trickling" compared to "non-diffuse-trickling" GA (135.2±56.4 vs. 191.4±77.8µm,p<0.001).

Conclusions: The results indicate an association of "diffuse-trickling" GA with systemic cardiovascular disorders in the younger study population. Together with the ocular morphological characteristics including a lobular appearance and a thin choroid, a vascular insufficiency at the level of the choroid may play a pathogenetic role in this distinct GA phenotype.

PMID: 24699379 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Mar 31. pii: S0002-9394(14)00167-6. doi: 10.1016/j.ajo.2014.03.013. [Epub ahead of print]

The Evolution of Laser Therapy in Ophthalmology: A Perspective on the Interactions between Photons, Patients, Physicians and Physicists The LXX Edward Jackson Memorial Lecture.

Blumenkranz MS.

PURPOSE: To present the evolution of laser therapy in modern ophthalmic practice DESIGN: Review of published experimental and clinical studies

METHODS: A review of the work of multiple investigators leading to the invention of the laser, its biophysical effects on ocular tissues from which it derives it name (light amplified stimulation of emitted radiation) , and the development of various laser based devices and methods to treat common ophthalmologic disorders with particular emphasis on new and emerging retinal and anterior segment applications.

RESULTS: Because the eye is optimized for the transmission of light and its transduction into neural signals, lasers are particularly well suited for ophthalmic therapy. This fact and the high demands for precision in therapy have inspired the development of highly sophisticated laser systems that have impacted the treatment of common diseases. These include diabetic retinopathy, age related macular degeneration, retinal venous occlusive disease, retinopathy of prematurity, optical aberrations including ametropia, cataract and glaucoma amongst others. Recent developments in scanning laser systems, including image guided systems with eye tracking, real-time feedback, as well as ultra-short pulse durations have enabled increased selectivity, precision and safety in ocular therapy. However, improved outcomes have been associated with increased cost of medical care, and attention to and optimization of their cost effectiveness will continue to be required in the future.

CONCLUSIONS: The invention and evolution of modern ophthalmic lasers have enhanced therapeutic options and can serve as a heuristic model for better understanding the process of innovation, including the societal benefits and also unintended consequences including increased costs.

PMID: 24699157 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2014 Apr 1. doi: 10.1111/aos.12326. [Epub ahead of print]

Effects of core vitrectomy in the treatment of age-related macular degeneration.

Schramm K, Mueller M, Koch FH, Singh P, Kohnen T, Koss MJ.

Abstract: To investigate the clinical efficacy and safety of an additional core vitrectomy to the standard therapy in patients with exudative age-related macular degeneration (ARMD). In this prospective, controlled, single-centre study, 50 eyes of 50 patients (mean age: 74.1 ± 7.1; median 74 (69/78)) with ARMD were enrolled and randomized 1:1 to group 1 - core vitrectomy additional to three times injections of ranibizumab (3x Rbz) and Group 2 - 3x Rbz (control). 1 16 of 25 eyes in Group 1(64%) and 12 of 25 (48%) in Group 2 had a posterior vitreous detachment (PVD) prior to start of the study. Changes in best-corrected visual acuity (BCVA) using ETDRS charts, central macular thickness and macular volume (OCT) as well as

the rate of reinjection with an OCT-based pro renata (PRN) protocol were monitored prospectively over 48 weeks. Forty-seven eyes completed follow-up at week 48. In Group 1, 4 of 24 lost 1 line of BCVA (16.7%) and 3 of 24 lost 2 lines (12.5%), whereas 17 of 24 gained more than 1 line (70.8%) and improved in average by 9.8 letters. In Group 2, 3 of 23 remained stable and 20 of 23 gained more than or exactly 1 line (78.3%), resulting in 14.3 letters, with no loss of lines. Central macular thickness decreased by 85.58 µm (28.8%) in Group 1 and by 121.43 µm (32.68%) in Group 2 compared with baseline. In Group 1, four patients received three additional and two patients, two additional Rbz injections. In Group 2, three patients received three additional, three patients two and 12 patients one additional Rbz injections. This yielded in an average injection rate of 3.66 in Group 1 and 4.17 in Group 2 over 48 weeks. Posterior vitreous detachment (PVD) was identified in Group 1 in 16 of 24 (66.7%) and in Group 2 in 12 of 23 (52.2%) patients at baseline. At week 48, 6 of 8 (75%) of the patients in Group 1 with initial attached vitreous showed a vitreal detachment, whereas only 1 of 11 (9%) in Group 2 had a new occurred detachment of the vitreous. No systemic or ocular adverse events were noticed. An initial core vitrectomy combined with a conventional ranibizumab injection regimen for exudative AMD patients was safe and lead to similar functional results with less intravitreal ranibizumab injections over 48 weeks..

PMID: 24690440 [PubMed - as supplied by publisher]

Biomed Opt Express. 2014 Feb 12;5(3):713-27. doi: 10.1364/BOE.5.000713. eCollection 2014.

Microstructure of subretinal drusenoid deposits revealed by adaptive optics imaging.

Meadway A, Wang X, Curcio CA, Zhang Y.

Abstract: Subretinal drusenoid deposits (SDD), a recently recognized lesion associated with progression of age-related macular degeneration, were imaged with adaptive optics scanning laser ophthalmoscopy (AO-SLO) and optical coherence tomography (AO-OCT). AO-SLO revealed a distinct en face structure of stage 3 SDD, showing a hyporeflective annulus surrounded reflective core packed with hyperreflective dots bearing a superficial similarity to the photoreceptors in the unaffected retina. However, AO-OCT suggested that the speckled appearance over the SDD rendered by AO-SLO was the lesion material itself, rather than photoreceptors. AO-OCT assists proper interpretation and understanding of the SDD structure and the lesions' impact on surrounding photoreceptors produced by AO-SLO and vice versa.

PMID: 24688808 [PubMed] PMCID: PMC3959830

Pathogenesis

Sci Transl Med. 2014 Apr 2;6(230):230ra44. doi: 10.1126/scitranslmed.3007616.

IL-18 attenuates experimental choroidal neovascularization as a potential therapy for wet age-related macular degeneration.

Doyle SL, Ozaki E, Brennan K, Humphries MM, Mulfaul K, Keaney J, Kenna PF, Maminishkis A, Kiang AS, Saunders SP, Hams E, Lavelle EC, Gardiner C, Fallon PG, Adamson P, Humphries P, Campbell M.

Abstract: Age-related macular degeneration (AMD) is the most common form of central retinal blindness globally. Distinct processes of the innate immune system, specifically activation of the NLRP3 inflammasome, have been shown to play a central role in the development of both "dry" and neovascular ("wet") forms of the disease. We show that the inflammatory cytokine interleukin-18 (IL-18) can regulate choroidal neovascularization formation in mice. We observed that exogenous administration of mature recombinant IL-18 has no effect on retinal pigment epithelial (RPE) cell viability, but that overexpression of pro-IL-18 or pro-IL-1β alone can cause RPE cell swelling and subsequent atrophy, a process that can be

inhibited by the promotion of autophagy. A direct comparison of local and systemic administration of mature recombinant IL-18 with current anti-VEGF (vascular endothelial growth factor)-based therapeutic strategies shows that IL-18 treatment works effectively alone and more effectively in combination with anti-VEGF therapy and represents a novel therapeutic strategy for the treatment of wet AMD.

PMID: 24695684 [PubMed - in process]

J Biol Chem. 2014 Apr 1. [Epub ahead of print]

Fibulin 2, a tyrosine O-sulfated protein, is up-regulated following retinal detachment.

Kanan Y, Brobst D, Han Z, Naash MI, Al-Ubaidi MR.

Abstract: Retinal detachment is the physical separation of the retina from the retinal pigment epithelium. It occurs during aging, trauma or during a variety of retinal disorders such as age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity or as complication following cataract surgery. This report investigates the role of fibulin 2, an extracellular component, in retinal detachment. A major mechanism for detachment resolution is enhancement of cellular adhesion between the retina and the retinal pigment epithelium and prevention of its cellular migration. This report shows that fibulin 2 is mainly present in the RPE, Bruch s membrane, choriocapillary, and to a lesser degree in retina. In vitro studies revealed the presence of two isoforms for fibulin 2. The small isoform located inside the cell while the large isoform present inside and outside the cells. Furthermore, fibulin 2 is post-translationally modified by tyrosine sulfation and the sulfated isoform is present outside the cell while the unsulfated pool is internally located. Interestingly, sulfated fibulin 2 significantly reduced the rate of cellular growth and migration. Finally, levels of fibulin 2 dramatically increased in the retinal pigment epithelium following retinal detachment, suggesting a direct role for fibulin 2 in the re-attachment of the retina to the retinal pigment epithelium. Understanding the role of fibulin 2 in enhancing retinal attachment is likely to help improve the current therapies or allow the development of new strategies for the treatment of this sight-threatening condition.

PMID: 24692557 [PubMed - as supplied by publisher]

Glia. 2014 Mar 31. doi: 10.1002/glia.22666. [Epub ahead of print]

Effect of glucocorticoids on neuronal and vascular pathology in a transgenic model of selective Müller cell ablation.

Shen W, Lee SR, Araujo J, Chung SH, Zhu L, Gillies MC.

Abstract: Retinal diseases such as macular telangiectasis type 2 (MacTel), age-related macular degeneration (AMD) and diabetic retinopathy (DR) affect both neurons and blood vessels. Treatments addressing both at the same time might have advantages over more specific approaches, such as vascular endothelial growth factor (VEGF) inhibitors, which are used to treat vascular leak but are suspected to have a neurotoxic effect. Here, we studied the effects of an intravitreal injection of triamcinolone acetonide (TA) in a transgenic model in which patchy Müller cell ablation leads to photoreceptor degeneration, vascular leak, and intraretinal neovascularization. TA was injected 4 days before Müller cell ablation. Changes in photoreceptors, microglia and Müller cells, retinal vasculature, differential expression of p75 neurotrophin receptor (p75NTR), tumor necrosis factor-α (TNFα), the precursor and mature forms of neurotrophin 3 (pro -NT3 and mature NT3) and activation of the p53 and p38 stress-activated protein kinase (p38/SAPK) signaling pathways were examined. We found that TA prevented photoreceptor degeneration and inhibited activation of microglial and Müller cells. TA attenuated Müller cell loss and inhibited overexpression of p75NTR , TNFα, pro-NT, and the activation of p53 and p38/SAPK signaling pathways. TA not only prevented the development of retinal vascular lesions but also inhibited fluorescein leakage from

established vascular lesions. TA inhibited overexpression of VEGF in transgenic mice but without affecting its basal level expression in the normal retina. Our data suggest that glucocorticoid treatment may be beneficial for treatment of retinal diseases such as MacTel, AMD, and DR that affect both neurons and the vasculature. GLIA 2014.

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Epidemiology

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Different hereditary contribution of the CFH gene between Polypoidal Choroidal Vasculopathy and Age-Related Macular Degeneration in Chinese Han people.

Huang L, Li Y, Guo S, Sun Y, Zhang C, Bai Y, Li S, Yang F, Zhao M, Wang B, Yu W, Zhao M, Khor CC, Li X.

Abstract Purpose: To investigate whether eleven variants in complement factor H gene contributed differently in patients with neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) of Chinese descent.

Methods: We performed a case-control study in a group of Chinese patients with nAMD (n=344) or PCV (n=368) and contrasted against an independent control group comprising 511 mild cataract patients without any evidence of age-related maculopathy. Association analysis of allele and genotype frequencies was performed for eleven haplotype-tagging single nucleotide polymorphisms (htSNPs) at the CFH locus (rs1061170, rs1329428, rs1410996, rs2284664, rs375396, rs529825, rs551397, rs7540032, rs800292, rs2274700, and rs1065489). Multinomial logistic regression analyses were performed to estimate and compare the effect of these 11 CFH polymorphisms on AMD and PCV, using the wild-type genotype as reference. Differences in the observed genotypic distributions between cases and controls were tested using chi-square tests, with age and gender adjusted for using logistic regression.

Results: CFH rs1065489 was not significantly associated with the nAMD phenotype in Chinese collections either on univariate or multivariate analysis ($p>0.05$ for all comparisons). The other ten SNPs of CFH were significantly associated with the nAMD phenotype. As for PCV, all 11 SNP markers were significantly associated with risk of PCV before or after correction for age and gender differences. Eight out of the eleven SNPs markers showed significant evidence of heterogeneity between AMD and PCV ($P<0.05$ for all comparisons).

Conclusion: Our data suggest that the genetic architecture at the CFH locus is complex with some markers showing significant skewing of the genotypes towards nAMD or PCV in Asians. This further supports the clinical observation that nAMD and PCV could have distinct pathogenesis mechanisms which will require larger studies to accurately dissect.

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ABCA1 rs1883025 Polymorphism Shows No Association with Neovascular Age-Related Macular Degeneration or Polypoidal Choroidal Vasculopathy in a Northern Chinese Population.

Li F, Li Y, Li M, Sun Y, Bai Y, Yang F, Guo J, Chen Y, Huang L, Li X.

Purpose: To analyze the association between ABCA1 rs1883025 variants with neovascular age-related

macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) in a northern Chinese population.

Methods: The study enrolled 900 subjects, including 300 controls, 300 cases with nAMD and 300 cases with PCV. Genomic DNA was extracted from venous blood leukocytes. Single-nucleotide polymorphisms in the ABCA1 (rs1883025) gene were genotyped by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

Results: The ABCA1 rs1883025 polymorphism was not significantly associated with nAMD (22.5%; $p > 0.05$) or PCV (20.8%; $p > 0.05$) in a northern Chinese population. The association remained insignificant after adjustment for age and gender differences ($p > 0.05$).

Conclusions: This study suggests that ABCA1 rs1883025 variants are not associated with nAMD or PCV in a Chinese population, which is likely due to an ethnic difference.

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Acta Clin Croat. 2013 Dec;52(4):448-52.

The role of diabetic retinopathy in blindness and poor sight in Split-Dalmatia County 2000-2010.

Galetović D, Olujić I, Znaor L, Bućan K, Karlica D, Lesin M, Susac T.

Abstract: Diabetic retinopathy is the fifth leading cause of blindness in the world. The aim of this study was to determine the number of blind persons in the Split-Dalmatia County in the 2000-2010 period and how many of them are blind due to diabetic retinopathy. Records of 160 members of the Association of the Blind in the Split-Dalmatia County, enrolled from 2000 to 2010, were retrospectively analyzed. The leading causes of blindness were diabetic retinopathy (25.6%), glaucoma (13.1%), retinal dystrophy (16.2%), and age related macular degeneration (11.8%). The annual incidence of blindness was 8.4/100,000 inhabitants. The largest number of the blind were found in the 70-80 (21.2%) to > 80 (24.3%) age group. Diabetic retinopathy was the cause of blindness in 24 (15%) men and 17 (10.6%) women. The annual incidence of diabetic retinopathy was 2.16 per 100,000. No case of blindness due to diabetic retinopathy was diagnosed in patients younger than 30 years of age, while the highest prevalence was found in the 70-80 age group (34%). Proliferative diabetic retinopathy was the cause of blindness in 92.7% and nonproliferative diabetic retinopathy in 7.3% of cases. Study results show that diabetic retinopathy remains the leading cause of blindness. Early identification of high-risk patients is the key factor in prevention and timely detection of ophthalmoscopic changes, thus enabling effective and duly treatment.

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Does toll-like receptor-3 (TLR-3) have any role in Indian AMD phenotype?

Sharma NK, Sharma K, Gupta A, Prabhakar S, Singh R, Gupta PK, Anand A.

Abstract: Age-related macular degeneration (AMD) is a devastating disease that results in irreversible central vision loss. TLRs signaling pathway has been found to play an important role in AMD pathogenesis as evidenced by several studies. The objective of the study was to determine the single nucleotide polymorphism (SNP) changes in TLR3 in North Indian AMD patients. We recruited 176 patients comprising 115 AMD patients and 61 controls. Real time PCR was used to evaluate the SNP changes at rs3775291 locus. Pearson's χ 2 test was used evaluate association between various groups. No significant association in genotype and allele frequency was found in AMD patients as compared to control. The results suggest that AMD pathology in North Indian AMD patients is not affected by TLR3 signaling but it could be

influenced by other genetic or environmental factors unique to North India.

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Age-related macular degeneration and the incidence of cardiovascular disease: a systematic review and meta-analysis.

Wu J, Uchino M, Sastry SM, Schaumberg DA.

IMPORTANCE: Research has indicated some shared pathogenic mechanisms between age-related macular degeneration (AMD) and cardiovascular disease (CVD). However, results from prior epidemiologic studies have been inconsistent as to whether AMD is predictive of future CVD risk.

OBJECTIVE: To systematically review population-based cohort studies of the association between AMD and risk of total CVD and CVD subtypes, coronary heart disease (CHD) and stroke.

DATA SOURCES: A systematic search of the PubMed and EMBASE databases and reference lists of key retrieved articles up to December 20, 2012 without language restriction.

DATA EXTRACTION: Two reviewers independently extracted data on baseline AMD status, risk estimates of CVD and methods used to assess AMD and CVD. We pooled relative risks using random or fixed effects models as appropriate.

RESULTS: Thirteen cohort studies (8 prospective and 5 retrospective studies) with a total of 1,593,390 participants with 155,500 CVD events (92,039 stroke and 62,737 CHD) were included in this meta-analysis. Among all studies, early AMD was associated with a 15% (95% CI, 1.08-1.22) increased risk of total CVD. The relative risk was similar but not significant for late AMD (RR, 1.17; 95% CI, 0.98-1.40). In analyses restricted to the subset of prospective studies, the risk associated with early AMD did not appreciably change; however, there was a marked 66% (95% CI, 1.31-2.10) increased risk of CVD among those with late AMD.

CONCLUSION: Whereas the results from all cohort studies suggest that both early and late AMD are predictive of a small increase in risk of future CVD, subgroup analyses limited to prospective studies demonstrate a markedly increased risk of CVD among people with late AMD. Retrospective studies using healthcare databases may have inherent methodological limitations that obscure such association. Additional prospective studies are needed to further elucidate the associations between AMD and specific CVD outcomes.

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Genetics

Genet Test Mol Biomarkers. 2014 Apr;18(4):245-52. doi: 10.1089/gtmb.2013.0368.

Roles of three common VEGF polymorphisms in the risk of age-related macular degeneration.

Liu Y, Hou S, Lang W, Dai D, Wang Z, Ji X, Li K, Zhang X, Zou Y, Wang J.

Abstract: Associations between vascular endothelial growth factor (VEGF) polymorphisms (rs833061, rs1413711, and rs3025039) and risk of age-related macular degeneration (AMD) have been extensively studied, but the currently available results are contentious rather than conclusive. Therefore, we performed the present meta-analysis to further assess the associations. Literature search in PubMed, Embase, and Web of Science databases was conducted until April 2013. The strength of the associations between VEGF

polymorphisms and AMD risk was estimated by pooled odds ratios (ORs) and 95% confidence intervals (CIs). Both models of fixed effects and random effects were performed to summarize the pooled ORs. All data were analyzed by Stata software 12.0. The meta-analysis results based on nine case-control studies with 2427 cases and 2037 controls showed that rs833061 had protective effects on AMD risk (TT vs. CT+CC: OR=0.58, 95% CI=0.41-0.81), whereas rs1413711 (TT vs. CT+CC: OR=1.46, 95% CI=1.10-1.93) and rs3025039 (TT vs. CC: OR=1.87, 95% CI=1.15-3.02; TT vs. CT+CC: OR=2.09, 95% CI=1.30-3.37) represented as risk factors for AMD. Subgroup analysis by ethnicity suggested significantly reduced risk in Caucasians (TT vs. CT+CC: OR=0.60, 95% CI=0.36-0.99; T vs. C: OR=0.89, 95% CI=0.78-1.00) and Asians (TT+CT vs. CC: OR=0.57, 95% CI=0.34-0.96; TT vs. CT+CC: OR=0.54, 95% CI=0.33-0.90) for rs833061, yet elevated risk in Caucasians (TT vs. CT+CC: OR=2.05, 95% CI=1.24-3.38) for rs1413711 and in Asians (TT vs. CC: OR=2.06, 95% CI=1.24-3.43; TT vs. CC: OR=2.34, 95% CI=1.42-3.89) for rs3025039. In stratified analysis by type of AMD, rs833061 was observed to decrease wet AMD risk, while rs1413711 and rs3025039 were found to increase the risk of wet AMD. Based on the currently available data, this meta-analysis suggests that the VEGF polymorphisms may be associated with risk of AMD, particularly wet AMD.

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Diet & lifestyle

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ESTIMATION OF ANTIOXIDANTS DIETARY INTAKE IN WET AGE-RELATED MACULAR DEGENERATION PATIENTS.

Bibiloni MD, Zapata ME, Aragón JA, Pons A, Olea JL, Tur JA.

Aims: The aim of this study was to estimate the intake of antioxidant nutrients in wet age-related macular degeneration (AMD) patients, a degenerative and progressive disorder of the macula, which is the central part of the retina, associated with central vision loss.

Methods: A sample (n = 52, 78.9 ± 6.6 years old, 40.4% females and 59.6% males) of patients diagnosed of AMD was interviewed. Anthropometric measurements, two 24- h recalls, a semi-quantitative food frequency questionnaire and a general questionnaire incorporating questions related to socio-demographic and lifestyle variables were used.

Results: Most of wet AMD patients showed inadequate antioxidant nutrient intake (< 2/3 of Recommended Dietary Intake, RDI), and more than 60% of patients showed serious deficient intake (< 1/3 RDI) of lutein and zeaxanthin. Most consumed antioxidant rich foods only represented low contributions to antioxidant intake. Although adiposity is a factor risk for AMD progression; the fat and saturated fatty acids (SFA) intake of study participants were higher than the recommendations; the prevalence of overweight was 61.9% men and 58.1% in women; and 83% of patients (90.5% men and 77.4% women) showed fat mass over the cut-off limits.

Conclusions: The food pattern of wet AMD patients should be improved by means of an increase in the consumption of antioxidant rich foods, and a decrease in SFA rich foods.

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Ocular Inflammation and Endoplasmic Reticulum Stress Are Attenuated by Supplementation with Grape Polyphenols in Human Retinal Pigmented Epithelium Cells and in C57BL/6 Mice.

Ha JH, Shil PK, Zhu P, Gu L, Li Q, Chung S.

Abstract: Inflammation and endoplasmic reticulum (ER) stress are common denominators for vision-threatening diseases such as diabetic retinopathy and age-related macular degeneration. Based on our previous study, supplementation with muscadine grape polyphenols (MGPs) alleviated systemic insulin resistance and proinflammatory responses. In this study, we hypothesized that MGPs would also be effective in attenuating ocular inflammation and ER stress. We tested this hypothesis using the human retinal pigmented epithelium (ARPE-19) cells and C57BL/6 mice. In ARPE-19 cells, tumor necrosis factor-α -induced proinflammatory gene expression of interleukin (IL)-1β, IL-6, and monocyte chemotactic protein-1 was decreased by 35.0, 68.8, and 62.5%, respectively, with MGP pretreatment, which was primarily due to the diminished mitogen-activated protein kinase activation and subsequent reduction of nuclear factor κ-B activation. Consistently, acute ocular inflammation and leukocyte infiltration were almost completely dampened (>95%) by MGP supplementation (100-200 mg/kg body weight) in C57BL/6 mice. Moreover, MGPs reduced inflammation-mediated loss of tight junctions and retinal permeability. To further investigate the protective roles of MGPs against ER stress, ARPE-19 cells were stimulated with thapsigargin. Pretreatment with MGPs significantly decreased the following: 1) ER stress-mediated vascular endothelial growth factor secretion (3.47 ± 0.06 vs. 1.58 ± 0.02 μg/L, $P < 0.0001$), 2) unfolded protein response, and 3) early apoptotic cell death (64.4 ± 6.85 vs. 33.7 ± 4.32%, $P = 0.0003$). Collectively, we have demonstrated that MGP is effective in attenuating ocular inflammation and ER stress. Our work also suggests that MGP may provide a novel dietary strategy to prevent vision-threatening retinal diseases.

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Protective effects of bilberry and lingonberry extracts against blue light-emitting diode light-induced retinal photoreceptor cell damage in vitro.

Ogawa K, Kuse Y, Tsuruma K, Kobayashi S, Shimazawa M, Hara H.

BACKGROUND: Blue light is a high-energy or short-wavelength visible light, which induces retinal diseases such as age-related macular degeneration and retinitis pigmentosa. Bilberry (Vaccinium myrtillus L.) and lingonberry (Vaccinium vitis-idaea) contain high amounts of polyphenols (anthocyanins, resveratrol, and proanthocyanidins) and thus confer health benefits. This study aimed to determine the protective effects and mechanism of action of bilberry extract (B-ext) and lingonberry extract (L-ext) and their active components against blue light-emitting diode (LED) light-induced retinal photoreceptor cell damage.

METHODS: Cultured murine photoreceptor (661 W) cells were exposed to blue LED light following treatment with B-ext, L-ext, or their constituents (cyanidin, delphinidin, malvidin, trans-resveratrol, and procyanidin B2). 661 W cell viability was assessed using a tetrazolium salt (WST-8) assay and Hoechst 33342 nuclear staining, and intracellular reactive oxygen species (ROS) production was determined using CM-H2DCFDA after blue LED light exposure. Activation of p38 mitogen-activated protein kinase (p38 MAPK), nuclear factor-kappa B (NF-kappaB), and LC3, an ubiquitin-like protein that is necessary for the formation of autophagosomes, were analyzed using Western blotting. Caspase-3/7 activation caused by blue LED light exposure in 661 W cells was determined using a caspase-3/7 assay kit.

RESULTS: B-ext, L-ext, NAC, and their active components improved the viability of 661 W cells and inhibited the generation of intracellular ROS induced by blue LED light irradiation. Furthermore, B-ext and L -ext inhibited the activation of p38 MAPK and NF-kappaB induced by blue LED light exposure. Finally, B-ext, L-ext, and NAC inhibited caspase-3/7 activation and autophagy.

CONCLUSIONS: These findings suggest that B-ext and L-ext containing high amounts of polyphenols exert protective effects against blue LED light-induced retinal photoreceptor cell damage mainly through inhibition of ROS production and activation of pro-apoptotic proteins.

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