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MD Research News

Issue 283

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Drug treatment

Graefes Arch Clin Exp Ophthalmol. 2016 Jun 4. [Epub ahead of print]

Psychological impact of anti-VEGF treatments for wet macular degeneration-a review.

Senra H, Ali Z, Balaskas K, Aslam T.

PURPOSE: To review the current literature on the psychological impact of anti-VEGF treatments for wet age-related macular degeneration (wAMD), in terms of patients' experiences of receiving these treatments, and the impact of these treatments for patients' mental health and quality of life.

METHODS: We critically analyzed current literature evaluating psychological impact of anti-VEGF treatments for wAMD. Primary searches of PubMed, Science Direct, and Web of Science were conducted in July and August of 2015. We reviewed all papers on the topic published until August 5, 2015.

RESULTS: Our literature search found 14 papers addressing the psychological impact of anti-VEGF treatments for wAMD. Results highlighted potential anxieties and experiences of pain caused by receiving regular intravitreal injections. A positive visual outcome of anti-VEGF therapy is associated with positive vision-related QOL outcomes, although such association seems to be dependent on improvements on visual acuity. In the literature reviewed, patients receiving anti-VEGF treatments showed a prevalence rate of depression between 20 and 26 %.

CONCLUSIONS: Although anti-VEGF treatments can cause some anxiety and being experienced as a stressful event, especially in the beginning of the treatment, preliminary findings suggest a potential benefit for long-term vision-related quality of life. Further longitudinal and qualitative research should bring more evidence on the positive and negative effects of these treatments on patients' long-term mental health.

PMID: 27262729 [PubMed - as supplied by publisher]

Ophthalmologe. 2016 Jun 6. [Epub ahead of print]

[Compliance of age related macular degeneration patients undergoing anti-VEGF therapy : Analysis and suggestions for improvement]. [Article in German]

Heimes B, Gunnemann F, Ziegler M, Gutfleisch M, Spital G, Pauleikhoff D, Lommatzsch A.

BACKGROUND: Activity-based treatment regimens with anti-vascular endothelial growth factor (anti-VEGF) are currently the gold standard for treatment of exudative age-related macular degeneration (nAMD). Whereas injection frequencies of approximately seven injections in the first year and six in the second year are expected with a pro re nata (PRN) regimen, retrospective real life observations have recorded significantly reduced numbers of injections. This study was carried out to investigate the reasons for the reduction in follow-up control appointments and to find out whether a telemedicine network could

influence the motivation and compliance for regular control examinations and treatment.

MATERIAL AND METHODS: The patient collective included 210 eyes from 191 patients with nAMD treated by anti-VEGF therapy in 2010 and 2011. The activity-based anti-VEGF treatment, control examinations and treatment intervals were performed according to the guidelines over a mean follow-up of 2 years. In another collective of 100 eyes from 100 patients with treatment of nAMD 2 groups were observed: 1 group with patients for whom control examinations were carried out close to home including an online transmission of the results to the treating retinal center and another group in which the patients had to be examined in the treatment center.

RESULTS: After 140 weeks 50 % of the patients in the first collective regularly attended control examinations and after 1 year the number was 79 %. After 2 years the probability of continuous supervision is given for only 62 % of the patients, whereas in 38 % the treatment was terminated. Of these patients treatment was terminated in 8 % due to valid criteria, whereas in 30 % of the patients the termination was unintentional. The main reason (38 %) for an unintentional termination of examination and treatment was the frequent and long journey. Patients in the second collective had a significantly higher compliance with respect to the control examinations ($p < 0.001$) and number of injections ($p = 0.02$) over the period of nearly 2 years due to the introduction of electronic transmission of images.

CONCLUSION: A long-term therapy of nAMD in the clinical routine can be achieved by a close relationship with the ophthalmologist, continuous follow-up controls and therapy cycles. A close telemedical networking between the ophthalmologist and the treatment center can lead to better patient compliance. Furthermore, the construction of such platforms represents a challenge not only for the treatment of nAMD but also for other diseases.

PMID: 27272633 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2016 Jun 9. [Epub ahead of print]

Cost-effectiveness of Aflibercept, Bevacizumab, and Ranibizumab for Diabetic Macular Edema Treatment: Analysis From the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trial.

Ross EL, Hutton DW, Stein JD, Bressler NM, Jampol LM, Glassman AR; Diabetic Retinopathy Clinical Research Network.

IMPORTANCE: Anti-vascular endothelial growth factor (VEGF) medicines have revolutionized diabetic macular edema (DME) treatment. A recent randomized clinical trial comparing anti-VEGF agents for patients with decreased vision from DME found that at 1 year aflibercept (2.0 mg) achieved better visual outcomes than repackaged (compounded) bevacizumab (1.25 mg) or ranibizumab (0.3 mg); the worse the starting vision, the greater the treatment benefit with aflibercept. However, aflibercept and ranibizumab, respectively, are approximately 31 and 20 times more expensive than bevacizumab.

OBJECTIVE: To examine the incremental cost-effectiveness ratios (ICERs) of aflibercept, bevacizumab, and ranibizumab for the treatment of DME.

DESIGN, SETTING, AND PARTICIPANTS: Post hoc analysis of efficacy, safety, and resource utilization data at 1-year follow-up from the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trial. Patients were enrolled from August 22, 2012, through August 28, 2013, and analysis was performed from August 21, 2014, through November 7, 2015.

MAIN OUTCOMES AND MEASURES: The ICERs for all trial participants and subgroups with baseline vision of approximate Snellen equivalent 20/32 to 20/40 (better vision) and baseline vision of approximate Snellen equivalent 20/50 or worse (worse vision). One-year trial data were used to calculate cost-effectiveness for 1 year for the 3 anti-VEGF agents; mathematical modeling was then used to project 10-year cost-effectiveness results.

RESULTS: The study included 624 participants (mean [SD] age, 60.6 [10.5] years; 45.7% female; 65.5% white), 209 in the aflibercept group, 207 in the bevacizumab group, and 208 in the ranibizumab group. For all participants, during 1 year, the ICERs of aflibercept and ranibizumab compared with bevacizumab were $1 110 000 per quality-adjusted life-year (QALY) and $1 730 000 per QALY, respectively. During 10 years, they were $349 000 per QALY and $603 000 per QALY, respectively. Compared with ranibizumab, aflibercept's ICER was $648 000 per QALY at 1 year and $203 000 per QALY at 10 years. For the subgroup with worse baseline vision, the 10-year ICERs of aflibercept and ranibizumab compared with bevacizumab were $287 000 per QALY and $817 000 per QALY, respectively. In eyes with decreased vision from DME, treatment costs of aflibercept and ranibizumab would need to decrease by 69% and 80%, respectively, to reach a cost-effectiveness threshold of $100 000 per QALY compared with bevacizumab during a 10-year horizon; for the subgroup with worse baseline vision, the costs would need to decrease by 62% and 84%, respectively.

CONCLUSIONS AND RELEVANCE: Aflibercept (2.0 mg) and ranibizumab (0.3 mg) are not cost-effective relative to bevacizumab for treatment of DME unless their prices decrease substantially. These results highlight the challenges that physicians, patients, and policymakers face when safety and efficacy results are at odds with cost-effectiveness results.

PMID: 27280850 [PubMed - as supplied by publisher]

J Ophthalmol. 2016;2016:6971831. Epub 2016 May 5.

Daily Optical Coherence Tomography Examinations after First Antivascular Endothelial Growth Factor Injections: An Interventional Case Series.

Novais EA, Badaró E, Hirai FE, Jorge FA, Leal P, Farah ME, Rodrigues EB.

Purpose: To evaluate daily spectral-domain optical coherence tomography (SD-OCT) changes in naive-treatment patients with diagnosis of exudative age-related macular degeneration (AMD) treated with intravitreous bevacizumab (1.25 mg), during a 30-day follow-up period.

Methods: In prospective, interventional study, SD-OCT was performed daily for 30 days after the first intravitreal injection. The baseline, initial-decrease, minimal, and final central retinal thicknesses (CRTs) were assessed.

Results: Nine eyes of nine patients with neovascular AMD were enrolled. The mean baseline CRT was 625.3 ± 182.5 μm, and the mean final CRT was 383.4 ± 163.0 μm (mean difference, 206.1 ± 167.6 μm), a difference that reached significance (P = 0.006). After the first injection, the initial decrease in the CRT was seen as an average of one day after injection (mean CRT, 503.6 ± 189.10 μm; P = 0.0431). The speed of the reduction in the CRT tended to decrease by day 17. The mean CRT was 336.5 ± 105.44 μm and the mean minimal CRT on day 30 was 320.75 ± 96.38 μm.

Conclusion: The CRT decreased early after the first injection. We observed a tendency for reductions in the speed with which the CRT decreased by day 17 after the first injection, which may affect retreatment regime.

PMID: 27274866 [PubMed] PMCID: PMC4871969

Graefes Arch Clin Exp Ophthalmol. 2016 Jun 11. [Epub ahead of print]

Two-year, prospective, multicenter study of the use of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in the clinical setting in France.

Korobelnik JF, Kodjikian L, Delcourt C, Gualino V, Leaback R, Pinchinat S, Velard ME.

PURPOSE: To evaluate patterns of use and long-term efficacy and safety of dexamethasone intravitreal implant (DEX implant) in the treatment of macular edema secondary to branch or central retinal vein

occlusion (BRVO, CRVO) in French clinical practice.

METHODS: A 24-month, prospective, multicenter, longitudinal, observational study (LOUVRE) conducted at 48 randomly selected sites in metropolitan France enrolled consecutive adult patients with macular edema following retinal vein occlusion (RVO) who were treated with DEX implant at baseline. Re-treatment with DEX implant and use of other RVO treatments was at the physician's discretion. The primary endpoint was the change in best-corrected visual acuity (BCVA) from baseline to month 6. Secondary endpoints included change in BCVA, intraocular pressure (IOP), adverse events, and RVO treatments administered through month 24.

RESULTS: The analysis population of 375 patients (53.9 % BRVO, 46.1 % CRVO) received a mean of 2.6 DEX implant injections over 2 years; mean time between injections was 6.6 months. Mean (SD) change in BCVA from baseline was 5.1 (19.0) letters at month 6 ($p < 0.001$) and 4.6 (22.3) letters at month 24 ($p < 0.001$). During the study, 208 patients (55.5 %) received treatment other than DEX implant for RVO, usually laser or ranibizumab therapy, with first use of other therapy occurring at a mean of 8.7 months. Mean change from baseline BCVA at month 6 was 5.5 letters ($p < 0.001$, $N = 254$) in patients who had received only DEX implant and 4.2 letters ($p = 0.006$, $N = 121$) in patients who had received additional other RVO treatment during the first 6 months. At month 24, mean change from baseline BCVA was +20.7 letters in patients treated with a single DEX implant only ($p < 0.001$), +4.9 letters in patients treated with ≥2 DEX implants only ($p = 0.029$), and +2.3 letters in patients treated with DEX implant and other RVO treatment ($p = 0.143$). The most common adverse events (incidence) were cataract progression (39.7 %) and increased IOP (34.4 %). No glaucoma incisional surgeries were required.

CONCLUSIONS: Efficacy and safety of DEX implant in the treatment of RVO-associated macular edema were demonstrated in the French clinical setting. Patients who switched from DEX implant to other RVO treatments did not have improved outcomes. The study is registered at ClinicalTrials.gov with the identifier NCT01618266.

PMID: 27286894 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2016 May 17;10:861-9. eCollection 2016.

Ranibizumab in monotherapy and combined with photodynamic therapy for retinal angiomatous proliferation.

Arias L, Gómez-Ulla F, Ruiz-Moreno JM.

PURPOSE: To compare the effects of intravitreal ranibizumab in monotherapy (group A) and combined with photodynamic therapy (PDT) with verteporfin (group B) in retinal angiomatous proliferation (RAP) treatment.

METHODS: This was a multicentric, prospective, randomized clinical study conducted with parallel groups. The study eye in both groups received ranibizumab on days 1, 30, and 60 (loading dose); group B received PDT additionally on day 1. Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity (VA) testing and optical coherence tomography were performed monthly, and fluorescein angiography and indocyanine green angiography were performed quarterly. Retreatment criteria were leakage in fluorescein angiography or indocyanine green angiography, mean foveal thickness increase ≥100 µm, or VA decrease ≥5 letters.

RESULTS: Twenty patients were recruited (ten patients in each group). Six eyes had previous treatment (three eyes in group A and three eyes in group B), so only 14 eyes were naïve. At 12-month follow-up, mean VA improved +1.5 letters in group A and +5.6 letters in group B (analysis of variance test; P>0.05). Two patients (20%) in both groups gained ≥15 letters (chi-square test; P>0.05). Mean changes in greatest linear dimension and in foveal thickness were not statistically significant between groups of treatment (analysis of variance test; P>0.05). Mean retreatments per patient were 1.8 (group A) and 0.9 (group B) (Mann-Whitney U-test; P>0.05). One patient died due to underlying disease not related to study medication.

CONCLUSION: Intravitreal ranibizumab administered in monotherapy or combined with PDT was

efficacious in terms of VA stabilization in patients with RAP.

PMID: 27274190 [PubMed] PMCID: PMC4876105

Mol Pharm. 2016 Jun 10. [Epub ahead of print]

PLGA microparticles entrapping chitosan-based nanoparticles for the ocular delivery of ranibizumab.

Elsaid N, Jackson TL, Elsaid Z, Alqathama A, Somavarapu S.

Abstract: Age-related macular degeneration (AMD) is the leading cause of certified vision loss worldwide. The standard treatment for neovascular AMD involves repeated intravitreal injections of therapeutic proteins directed against vascular endothelial growth factor, such as ranibizumab. Biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA), form delivery vehicles which can be used to treat posterior segment eye diseases, but suffer from poor protein loading and release. This work describes a 'system-within-system', PLGA microparticles incorporating chitosan-based nanoparticles, for improved loading and sustained intravitreal delivery of ranibizumab. Chitosan-N-acetyl-L-cysteine (CNAC) was synthesized and its synthesis confirmed using FT-IR and 1H NMR. Chitosan-based nanoparticles comprised of CNAC, CNAC/tripolyphosphate (CNAC/TPP), chitosan, chitosan/TPP (chit/TPP) or chit/TPP-hyaluronic acid (chit/TPP-HA) were incorporated in PLGA microparticles using a modified w/o/w double emulsion method. Nanoparticles and final nanoparticles-within-microparticles were characterized for their protein-nanoparticle interaction, size, zeta potential, morphology, protein loading, stability, in vitro release, in vivo anti-angiogenic activity and effects on cell viability. The prepared nanoparticles were 17 - 350 nm in size and had zeta potentials of -1.4 to +12 mV. Microscopic imaging revealed spherical nanoparticles on the surface of PLGA microparticles for preparations containing chit/TPP, CNAC and CNAC/TPP. Ranibizumab entrapment efficiency in the preparations varied between 13 - 69% and was highest for the PLGA microparticles containing CNAC nanoparticles. This preparation also showed the slowest release with no initial burst release compared to all other preparations. Incorporation of TPP to this formulation increased the rate of protein release and reduced entrapment efficiency. PLGA microparticles containing chit/TPP-HA showed the fastest and near-complete release of ranibizumab. All of the prepared empty particles showed no effect on cell viability up to a concentration of 12.5 mg/mL. Ranibizumab released from all preparations maintained its structural integrity and in vitro activity. The chit/TPP-HA preparation enhanced anti-angiogenic activity and may provide a potential biocompatible platform for enhanced anti-angiogenic activity in combination with ranibizumab. In conclusion, the PLGA microparticles containing CNAC nanoparticles showed significantly improved ranibizumab loading and release profile. This novel drug delivery system may have potential for improved intravitreal delivery of therapeutic proteins, thereby reducing the frequency, risk and cost of burdensome intravitreal injections.

PMID: 27286558 [PubMed - as supplied by publisher]

J Pharm Pharmacol. 2016 Jun 10. [Epub ahead of print]

Dexamethasone - PAMAM dendrimer conjugates for retinal delivery: preparation, characterization and in vivo evaluation.

Yavuz B, Bozdağ Pehlivan S, Sümer Bolu B, Nomak Sanyal R, Vural İ, Ünlü N.

OBJECTIVE: Ocular diseases affecting retina, such as diabetic retinopathy (DR), age-related macular degeneration (AMD) and glaucoma are the major causes of blindness, and their treatment is still a challenge due to the special structure of the eye. The purpose of this study was to prepare a sustained release DEX conjugate formulation with enhanced ocular permeation using poly(amidoamine) (PAMAM) dendrimers and to evaluate the effects of conjugation on DEX release and ocular residence time.

METHODS: PAMAM G3.5 and PAMAM G4.5 dendrimers were used to prepare DEX conjugates, and

conjugation was confirmed using 1 H-NMR. Formulations were evaluated in terms of drug release in the presence of ocular enzymes and cytotoxicity on ARPE19 cell lines. Fluorotron analysis was performed and ocular pharmacokinetic properties of DEX-PAMAM conjugates were studied in Sprague Dawley rats following intravitreal and subconjunctival applications.

KEY FINDINGS: The results indicated that DEX-PAMAM conjugates were able to enhance ocular permeability and ocular tissue levels of DEX following subconjunctival injection, and results were encouraging when compared to the literature that has reported DEX getting cleared from vitreous in 3 h.

CONCLUSION: Current studies are focused on formulation improvement to enhance hydrolysis and clearance time.

PMID: 27283886 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2016 Jun 8. [Epub ahead of print]

ACTINOMYCES NEUII ENDOPHTHALMITIS AFTER INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTION.

Sahni S, Waston RM, Sheth VS.

PURPOSE: To describe a case of acute endophthalmitis caused by Actinomyces neuii after intravitreal anti-vascular endothelial growth factor injection.

METHODS: Observational case report, review of published literature.

RESULTS: A 67-year-old white man with wet age-related macular degeneration developed endophthalmitis secondary to A. neuii on the 10th day after intravitreal anti-vascular endothelial growth factor injection. Both anterior chamber and vitreous cultures were positive for A. neuii. He was treated successfully with intravitreal injection of vancomycin and ceftazidime.

CONCLUSION: This is the first published report of culture-positive endophthalmitis caused by A. neuii after intravitreal injection.

PMID: 27280342 [PubMed - as supplied by publisher]

Prescrire Int. 2016 May;25(171):132-3.

Ranibizumab or bevacizumab in AMD?

Abstract: The Italian independent drug bulletin Informazioni sui Farmaci, a member of the International Society of Drug Bulletins (ISDB), published a review comparing ranibizumab versus bevacizumab for age-related macular degeneration (AMD). Its conclusion differs from that of Prescrire's review, published in issue 163. Giulio Formoso and Maria Font have offered on behalf of Informazioni sui Farmacito present their evaluations. The position of Informazioni sui Farmaci is recapped below, and an English translation of the full article published in the Italian bulletin is available at english.prescrire.org. Giulio Formoso and Maria Font's letter is followed by a few points outlining Prescrire's position, already set out in detail in issue 163.

PMID: 27280201 [PubMed - in process]

Am J Ophthalmol. 2016 Jun 7. [Epub ahead of print]

Response of Pigment Epithelial Detachment to Anti-Vascular Endothelial Growth Factor Treatment in Age-Related Macular Degeneration.

Cho HJ, Kim HS, Lee DW.

PMID: 27287630 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2016 Jun 9. [Epub ahead of print]

Response to the letter to the editor: Comparison of intravitreal aflibercept and ranibizumab injections on subfoveal and peripapillary choroidal thickness in eyes with neovascular age-related macular degeneration.

Yun C, Oh J.

PMID: 27282873 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2016 Jun 4. [Epub ahead of print]

Conversion to Aflibercept After Prior Anti-VEGF Therapy for Persistent Diabetic Macular Edema.

Călugăru D, Călugăru M.

PMID: 27270364 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2016 Jun 4.[Epub ahead of print]

Conversion to Aflibercept After Prior Anti-VEGF Therapy for Persistent Diabetic Macular Edema.

Rahimy E, Shahlaee A, Khan MA, Ying GS, Maguire JI, Ho AC, Regillo CD, Hsu J.

PMID: 27270363 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2016 Jun 2. [Epub ahead of print]

Short-Term Changes in Choroidal Thickness After Aflibercept Therapy for Neovascular Age-Related Macular Degeneration.

Koizumi H, Yamamoto A, Maruko I, Okada AA, Iida T, Kano M, Saito M, Sekiryu T, Kawasaki R.

PMID: 27265886 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2016 Jun 1. [Epub ahead of print]

Short-Term Changes in Choroidal Thickness After Aflibercept Therapy for Neovascular Age-Related Macular Degeneration.

Uzun S, Pehlivan E.

PMID: 27262619 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2016 Jun 9. [Epub ahead of print]

CORRELATION OF SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY AND CLINICAL ACTIVITY IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Liang MC, de Carlo TE, Baumal CR, Reichel E, Waheed NK, Duker JS, Witkin AJ.

PURPOSE: To characterize the features of choroidal neovascularization (CNV) in neovascular age-related

macular degeneration with spectral domain optical coherence tomography angiography (OCTA) and to determine whether OCTA can be used to determine clinical activity of CNV.

METHODS: Observational, retrospective, consecutive case series.

RESULTS: Optical coherence tomography angiography revealed CNV in 28 eyes (62.2%) while 17 eyes (37.8%) did not demonstrate CNV vessels. Choroidal neovascularization was classified as well circumscribed in 12 eyes (42.8%) and poorly circumscribed in 16 eyes (57.2%). Twenty-two eyes with a CNV on OCTA were clinically active, whereas six eyes with visible CNV on OCTA were clinically inactive. Of the 17 eyes that did not have evidence of CNV on OCTA imaging, 14 were clinically inactive and 3 were clinically active. Presence of CNV on OCTA correlated with clinical activity and absence of CNV correlated with inactivity ($P < 0.0001$).

CONCLUSION: Optical coherence tomography angiography is a noninvasive imaging technique that can be used to visualize blood flow comprising CNV. Optical coherence tomography angiography detects CNV vessels in some albeit not all eyes with neovascular age-related macular degeneration. Although the presence or absence of CNV vessels on OCTA highly correlated with clinical activity of CNV, the morphologic appearance of CNV on OCTA did not have significant correlation with clinical activity.

PMID: 27285456 [PubMed - as supplied by publisher]

Eye (Lond). 2016 Jun 10. [Epub ahead of print]

Revisiting the role of erythropoietin for treatment of ocular disorders.

Shirley Ding SL, Leow SN, Munisvaradass R, Koh EH, Bastion ML, Then KY, Kumar S, Mok PL.

Abstract: Erythropoietin (EPO) is a glycoprotein hormone conventionally thought to be responsible only in producing red blood cells in our body. However, with the discovery of the presence of EPO and EPO receptors in the retinal layers, the EPO seems to have physiological roles in the eye. In this review, we revisit the role of EPO in the eye. We look into the biological role of EPO in the development of the eye and the physiologic roles that it has. Apart from that, we seek to understand the mechanisms and pathways of EPO that contributes to the therapeutic and pathological conditions of the various ocular disorders such as diabetic retinopathy, retinopathy of prematurity, glaucoma, age-related macular degeneration, optic neuritis, and retinal detachment. With these understandings, we discuss the clinical applications of EPO for treatment of ocular disorders, modes of administration, EPO formulations, current clinical trials, and its future directions.

PMID: 27285322 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2016 May 18;9(5):725-9. eCollection 2016.

Choroidal thickness measurements with optical coherence tomography in branch retinal vein occlusion.

Coban-Karatas M, Altan-Yaycioglu R, Ulas B, Sizmaz S, Canan H, Sariturk C.

AIM: To evaluate central macular thickness (CMT) and mean choroidal thickness (MCT) in eyes with branch retinal vein occlusion (BRVO), before and after ranibizumab treatment using spectral domain-optical coherence tomography (SD-OCT).

METHODS: Forty-two patients with unilateral BRVO and macular edema were included in this study. There were 25 men and 17 women. Using SD-OCT, choroidal thickness was measured at 500 μm intervals up to 1500 μm temporal and nasal to the fovea. MCT was calculated based on the average of the 7 locations. All the eyes with BRVO were treated with intravitreal ranibizumab (0.5 mg/0.05 mL). Comparisons between the BRVO and fellow eyes were analyzed using Mann-Whitney U test. Pre-injection and post-injection

measurements were analyzed using Wilcoxon test and repeated measure analysis.

RESULTS: At baseline, there was a significant difference between the BRVO and fellow eyes in MCT [BRVO eyes 245 (165-330) µm, fellow eyes 229 (157-327) µm] and CMT [BRVO eyes 463 (266-899) µm, fellow eyes 235 (148-378) µm (P=0.041, 0.0001, respectively)]. Following treatment, CMT [295 (141-558) µm] and MCT [229 (157-329) µm] decreased significantly compared to the baseline measurements (P=0.001, 0.006, respectively). Also BCVA (logMAR) improved significantly (P=0.0001) in the BRVO eyes following treatment. After treatment CMT [BRVO eyes 295 (141-558) µm, fellow eyes 234 (157-351) µm] and MCT [BRVO eyes 229 (157-329) µm, fellow eyes 233 (162-286) µm] values did not reveal any significant difference in BRVO eyes and fellow eyes (P=0.051, 0.824, respectively).

CONCLUSION: In eyes with BRVO, CMT and MCT values are greater than the fellow eyes, and decrease significantly following ranibizumab injection.

PMID: 27275430 [PubMed] PMCID: PMC4886886

Pathogenesis

Hum Mol Genet. 2016 Jun 6. [Epub ahead of print]

The Unconventional Secretion of ARMS2.

Kortvely E, Hauck SM, Behler J, Ho N, Ueffing M.

Abstract: Age-related maculopathy susceptibility 2 (ARMS2) is a small (11 kDa), primate-specific protein found in the extracellular matrix of the choroid layer in the eye. Variants in the corresponding genetic locus are highly associated with age-related macular degeneration (AMD), a leading cause of blindness in the elderly. So far, the physiological function of ARMS2 has remained enigmatic. It has been demonstrated that ARMS2 is a genuine secreted protein devoid of an N-terminal leader sequence, yet the mechanism how it exits the cells and enters the choroidal matrix is not understood.Here we show that ARMS2 efficiently recruits lectin chaperones from the cytosol and colocalizes with calnexin-positive and PDI-negative vesicle-like structures. Site-directed mutagenesis revealed critical elements for this interaction. Mutant forms proving unable to interact with the calnexin/calreticulin system failed secretion. On the other hand, blocking the ER to Golgi transport with BFA had no effect on ARMS2 secretion.As we found ARMS2 colocalizing with GRASP65, a marker for unconventional protein secretion, autophagic factors are likely to be key in its export. Interleukin-1ß (IL-1ß) is the most established example of secretory autophagy. Co-expression experiments, however, suggest that the transport of ARMS2 is different from that of IL-1ß. In conclusion, in this work we show that ARMS2 is externalized via an unconventional pathway bypassing Golgi. Its intracellular separation from the classical secretion pathway suggests that the maturation of the protein requires a specific biochemical niche and/or may be needed to impede the premature formation of unwanted protein-protein interactions.

PMID: 27270414 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2016 Jun 7;16(1):80.

T-helper-associated cytokines expression by peripheral blood mononuclear cells in patients with polypoidal choroidal vasculopathy and age-related macular degeneration.

Yu Y, Ren XR, Wen F, Chen H, Su SB.

BACKGROUND: Immune responses play a key role in the pathogenesis and progression of polypoidal choroidal vasculopath (PCV) and age-related macular degeneration (AMD). In this study, we determined the Th cell-associated immune responses by measuring the cytokine expression of peripheral blood mononuclear cells (PBMC) in both PCV and neovascular AMD (nAMD) patients.

METHODS: Twenty-seven nAMD patients, 33 PCV patients and a gender- and age-matched group of 18 healthy individuals were involved in this study. The Th-cell cytokine profiles including levels of interferon-gamma (INF-γ), interleukin (IL)-17A and IL-4 in cultures of PBMCs were determined by enzyme-linked immunosorbent assay (ELISA).

RESULTS: IFN-γ,IL-17A and IL-4 production was significantly increased after stimulation with PHA. The levels of IFN-γ and IL-4 in PHA-stimulated cultures were higher in PCV and nAMD patients than that in healthy controls ($P = 0.038$,$P = 0.014$), while no difference was found between PCV and nAMD (all $P > 0.05$). No significant difference in IL-17A level in PHA-stimulated cultures was found among PCV, nAMD and control groups ($P > 0.05$).

CONCLUSIONS: These findings suggest that circulating IFN-γ and IL-4 producing Th1 and Th2 cells may involve in the pathogenesis of PCV and nAMD. PCV may have the similar immune responses with nAMD.

PMID: 27266510 [PubMed - in process] PMCID: PMC4895798

Acta Ophthalmol. 2016 Jun 11. [Epub ahead of print]

Attenuation of iron-binding proteins in ARPE-19 cells reduces their resistance to oxidative stress.

Karlsson M, Kurz T.

PURPOSE: Oxidative stress-related damage to retinal pigment epithelial (RPE) cells is an important feature in the development of age-related macular degeneration. Iron-catalysed intralysosomal production of hydroxyl radicals is considered a major pathogenic factor, leading to lipofuscin formation with ensuing depressed cellular autophagic capacity, lysosomal membrane permeabilization and apoptosis. Previously, we have shown that cultured immortalized human RPE (ARPE-19) cells are extremely resistant to exposure to bolus doses of hydrogen peroxide and contain considerable amounts of the iron-binding proteins metallothionein (MT), heat-shock protein 70 (HSP70) and ferritin (FT). According to previous findings, autophagy of these proteins depresses lysosomal redox-active iron. The aim of this study was to investigate whether up- or downregulation of these proteins would affect the resistance of ARPE-19 cells to oxidative stress.

METHODS: The sensitivity of ARPE-19 cells to H2 O2 exposure was tested following upregulation of MT, HSP70 and/or FT by pretreatment with ZnSO4 , heat shock or FeCl3 , as well as siRNA-mediated downregulation of the same proteins.

RESULTS: Upregulation of MT, HSP70 and FT did not improve survival following exposure to H2 O2 . This was interpreted as existence of an already maximal protection. Combined siRNA-mediated attenuation of both FT chains (H and L), or simultaneous downregulation of all three proteins, made the cells significantly more susceptible to oxidative stress confirming the importance of iron-binding proteins.

CONCLUSION: The findings support our hypothesis that the oxidative stress resistance exhibited by RPE cells may be explained by a high autophagic influx of iron-binding proteins that would keep levels of redox-active lysosomal iron low.

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Isolation, culture and characterization of primary mouse RPE cells.

Fernandez-Godino R, Garland DL, Pierce EA.

Abstract: Mouse models are powerful tools for the study of ocular diseases. Alterations in the morphology and function of the retinal pigment epithelium (RPE) are common features shared by many ocular disorders. We report a detailed protocol to collect, seed, culture and characterize RPE cells from mice. We

describe a reproducible method that we previously developed to collect and culture murine RPE cells on Transwells as functional polarized monolayers. The collection of RPE cells takes ~3 h, and the cultures mimic in vivo RPE cell features within 1 week. This protocol also describes methods to characterize the cells on Transwells within 1-2 weeks by transmission and scanning electron microscopy (TEM and SEM, respectively), immunostaining of vibratome sections and flat mounts, and measurement of transepithelial electrical resistance. The RPE cell cultures are suitable to study the biology of the RPE from wild-type and genetically modified strains of mice between the ages of 10 d and 12 months. The RPE cells can also be manipulated to investigate molecular mechanisms underlying the RPE pathology in the numerous mouse models of ocular disorders. Furthermore, modeling the RPE pathology in vitro represents a new approach to testing drugs that will help accelerate the development of therapies for vision-threatening disorders such as macular degeneration (MD).

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Proc Natl Acad Sci U S A. 2016 Jun 6. [Epub ahead of print]

Photodegradation of retinal bisretinoids in mouse models and implications for macular degeneration.

Ueda K, Zhao J, Kim HJ, Sparrow JR.

Abstract: Adducts of retinaldehyde (bisretinoids) form nonenzymatically in photoreceptor cells and accumulate in retinal pigment epithelial (RPE) cells as lipofuscin; these fluorophores are implicated in the pathogenesis of inherited and age-related macular degeneration (AMD). Here we demonstrate that bisretinoid photodegradation is ongoing in the eye. High-performance liquid chromatography (HPLC) analysis of eyes of dark-reared and cyclic light-reared wild-type mice, together with comparisons of pigmented versus albino mice, revealed a relationship between intraocular light and reduced levels of the bisretinoids A2E and A2-glycero-phosphoethanolamine (A2-GPE). Analysis of the bisretinoids A2E, A2-GPE, A2-dihydropyridine-phosphatidylethanolamine (A2-DHP-PE), and all-trans-retinal dimer-phosphatidylethanolamine (all-trans-retinal dimer-PE) also decreases in albino Abca4-/- mice reared in cyclic light compared with darkness. In albino Abca4-/- mice receiving a diet supplemented with the antioxidant vitamin E, higher levels of RPE bisretinoid were evidenced by HPLC analysis and quantitation of fundus autofluorescence; this effect is consistent with photooxidative processes known to precede bisretinoid degradation. Amelioration of outer nuclear layer thinning indicated that vitamin E treatment protected photoreceptor cells. Conversely, in-cage exposure to short-wavelength light resulted in reduced fundus autofluorescence, decreased HPLC-quantified A2E, outer nuclear layer thinning, and increased methylglyoxal (MG)-adducted protein. MG was also released upon bisretinoid photodegradation in cells. We suggest that the lower levels of these diretinal adducts in cyclic light-reared and albino mice reflect photodegradative loss of bisretinoid. These mechanisms may underlie associations among AMD risk, oxidative mechanisms, and lifetime light exposure.

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Genetics

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Association of Combined Complement Factor H Y402H and ARMS/LOC387715 A69S Polymorphisms with Age-related Macular Degeneration: A Meta-analysis.

Jabbarpoor Bonyadi MH, Yaseri M, Bonyadi M, Soheilian M, Karimi S.

PURPOSE: Complement factor H (CFH) Y402H (rs1061170) and age-related maculopathy susceptibility2 (ARMS2)/LOC387715 A69S (rs10490924) polymorphisms shown to have significant association with age-related macular degeneration (AMD). In this meta-analysis, we pooled the results of the available

association studies between combined ARMS2/LOC387715A69S-CFHY402H genotypes and AMD to estimate the possible synergistic or multiplicative effects.

METHODS: Heterogeneity of studies was evaluated using the Cochran Q-test and the I-square index. To modify the heterogeneity in the variables, we used random effects model. Meta-analysis was performed using STATA. To estimate the additive or supra-additive effects, we calculated relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), synergy index (S), and multiplicative index (V).

RESULTS: We included eight studies with 2915 AMD patients and 3505 control subjects. Considering the GGTT genotypes as reference lines, the pooled AMD Odds Ratios for stratified combined genotypes were 2.32 (95% CI 1.64-3.28) for GGnon-TT, 2.49 (95% CI 1.72-3.60) for non-GGTT, and 7.82 (95% CI 5.09-12.00) for non-GGnon-TT. Pooled synergy analysis revealed RERI = 4.08 (95% CI 3.15-5.27), AP = 0.50 (95% CI 0.42-0.57), S = 2.31 (95% CI 1.9-2.82), and V = 1.21 (95% CI 0.93-1.49).

CONCLUSION: This analysis revealed the synergistic and positive multiplicative effect of these two genes indicating that there is a common pathway of ARMS2/LOC387715 and CFH in AMD pathogenesis which may be the complement system pathway.

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Diet, lifestyle & low vision

Invest Ophthalmol Vis Sci. 2016 Jun 1;57(7):3032-8.

Illness Cognitions and Coping Self-Efficacy in Depression Among Persons With Low Vision.

Sturrock BA, Xie J, Holloway EE, Hegel M, Casten R, Mellor D, Fenwick E, Rees G.

PURPOSE: To investigate the mediating role of coping self-efficacy (CSE) between two types of illness cognitions (i.e., acceptance and helplessness) and depressive symptoms in persons with low vision.

METHODS: This was a single-group, cross-sectional study. Patients with visual acuity < 6/12 in the better eye and at least minimal depressive symptoms (≥5 on the Patient Health Questionnaire-9 [PHQ-9]) were recruited from vision rehabilitation services and participated in telephone-administered structured interviews at one time point. Measures were the PHQ-9, CSE Scale, and Illness Cognition Questionnaire. Structural equation modeling (SEM) devised the causal flow of illness cognitions and their observed indirect effects on depressive symptoms via the CSE mediators: problem focused, emotion focused, and social support.

RESULTS: The study comprised 163 patients (mean age 62 years; 61% female), most with age-related macular degeneration (26%) and moderate vision impairment (44%, <6/18-6/60). Structural equation modeling indices indicated a perfect fit ($\chi 2 < 0.001$, $P = 1.00$), accounting for 55% of the variance in depressive symptoms. Lower levels of acceptance and higher levels of helplessness illness cognitions were associated with lower self-efficacy in problem-focused coping ($\beta = 0.38$, $P < 0.001$, $\beta = -0.28$, $P < 0.01$, respectively), which in turn was associated with greater depressive symptom severity ($\beta = -0.54$, $P < 0.001$).

CONCLUSIONS: Lack of acceptance and greater helplessness relating to low vision led to a lack of perceived capability to engage in problem-focused coping, which in turn promoted depressive symptoms. Third-wave cognitive-behavioral treatments that focus on acceptance may be efficacious in this population.

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An exploratory study evaluating the effects of macular carotenoid supplementation in various

retinal diseases.

Crosby-Nwaobi R, Hykin P, Peto T, Sivaprasad S.

PURPOSE: The aim of this study was to assess the impact of daily oral supplementation with Macushield (10 mg/d meso-zeaxanthin, 10 mg/d lutein, and 2 mg/d zeaxanthin) on eye health in patients with retinal diseases by assessing the macular pigment (MP) profile, the visual function, and the quality of life.

METHODS: Fifty-one patients with various retinal diseases were supplemented daily and followed up for 6 months. The MP optical density was measured using the customized heterochromatic flicker photometry and dual-wavelength autofluorescence. Visual function was evaluated by assessing the change in best corrected visual acuity, contrast sensitivity, and glare sensitivity in mesopic and photopic conditions. Vision-related and general quality of life changes were determined using the National Eye Insititute- Visual Function Questionnaire-25 (NEI-VFQ-25) and EuroQoL-5 dimension questionnaires.

RESULTS: A statistically significant increase in the MP optical density was observed using the dual-wavelength autofluorescence ($P=0.04$) but not with the customized heterochromatic flicker photometry. Statistically significant ($P<0.05$) improvements in glare sensitivity in low and medium spatial frequencies were observed at 3 months and 6 months. Ceiling effects confounded other visual function tests and quality of life changes.

CONCLUSION: Supplementation with the three carotenoids enhances certain aspects of visual performance in retinal diseases.

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