

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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## Drug treatment

**J Control Release. 2015 Jan 5;200C:71-77. [Epub ahead of print]**

### **Light-responsive nanoparticle depot to control release of a small molecule angiogenesis inhibitor in the posterior segment of the eye.**

Huu VA, Luo J, Zhu J, Zhu J, Patel S, Boone A, Mahmoud E, McFearin C, Olejniczak J, de Gracia Lux C, Lux J, Fomina N, Huynh M, Zhang K, Almutairi A.

**Abstract:** Therapies for macular degeneration and diabetic retinopathy require intravitreal injections every 4-8 weeks. Injections are uncomfortable, time-consuming, and carry risks of infection and retinal damage. However, drug delivery via noninvasive methods to the posterior segment of the eye has been a major challenge due to the eye's unique anatomy and physiology. Here we present a novel nanoparticle depot platform for on-demand drug delivery using a far ultraviolet (UV) light-degradable polymer, which allows noninvasively triggered drug release using brief, low-power light exposure. Nanoparticles stably retain encapsulated molecules in the vitreous, and can release cargo in response to UV exposure up to 30 weeks post-injection. Light-triggered release of nintedanib (BIBF 1120), a small molecule angiogenesis inhibitor, 10 weeks post-injection suppresses choroidal neovascularization (CNV) in rats. Light-sensitive nanoparticles are biocompatible and cause no adverse effects on the eye as assessed by electroretinograms (ERG), corneal and retinal tomography, and histology.

PMID: 25571784 [PubMed - as supplied by publisher]

**Invest Ophthalmol Vis Sci. 2014 Dec 18;56(1):330-8.**

### **Intravitreal Sirolimus for the Treatment of Geographic Atrophy: Results of a Phase I/II Clinical Trial.**

Petrou PA, Cunningham D, Shimel K, Harrington M, Hammel K, Cukras CA, Ferris FL, Chew EY, Wong WT.

**PURPOSE:** To investigate the safety and effects of intravitreal sirolimus for the potential treatment of geographic atrophy (GA).

**METHODS:** The study was a single-center, open-label, phase I/II trial enrolling six participants with bilateral GA treated with intravitreal sirolimus in only one randomly assigned eye, with the fellow eye as control. The primary efficacy outcome measure was the change in total GA area from baseline on color fundus photography (CFP); secondary outcomes included changes in GA area on fundus autofluorescence (FAF), visual acuity, central retinal thickness (CRT), and macular sensitivity from baseline.

**RESULTS:** Although no systemic adverse events were attributed to treatment, two of six participants had ocular adverse events that were possibly associated. The treated eye of one participant developed

abnormal paralesional changes on FAF that were associated with accelerated retinal thinning. This accelerated retinal thinning was also seen in the treated eye of a second participant. Because of concern that these events were associated with treatment, treatment was suspended. Comparisons of treated and fellow eyes for change in visual acuity, change in GA area, and change in CRT showed no evidence of treatment benefit and generally favored the untreated fellow eye.

**CONCLUSIONS:** While paralesional FAF changes and rapid retinal thinning observed are potentially part of the natural course of GA, they may possibly be related to treatment. No general evidence of anatomical or functional benefit was detected in treated eyes. Further data on intravitreal sirolimus for GA treatment will be available from a larger phase II trial. (ClinicalTrials.gov number, NCT01445548.).

PMID: 25525171 [PubMed - in process] PMCID: PMC4294293

## **Acta Ophthalmol. 2015 Jan 11. [Epub ahead of print]**

### **Association between choroidal thickness and the response to intravitreal ranibizumab injection in age-related macular degeneration.**

Shin JY, Kwon KY, Byeon SH.

**PURPOSE:** To investigate the relationship between the choroidal thicknesses of eyes of patients with age-related macular degeneration (AMD) and the outcomes of intravitreal ranibizumab injection.

**METHODS:** We reviewed the medical records of 141 consecutive eyes (80 with typical neovascular AMD and 61 with polypoidal choroidal vasculopathy [PCV]) treated by intravitreal ranibizumab and 121 normal control eyes matched in terms of age and spherical equivalent (SE). Eyes of patients were divided into three subgroups with thin, medium and thick choroids. We investigated the relationships between choroidal thickness and treatment outcomes of intravitreal ranibizumab.

**RESULTS:** In eyes with typical neovascular AMD, thin choroids were associated with older age (linear regression;  $p < 0.0001$ ) and larger choroidal neovascularization (CNV) lesions ( $p = 0.049$ ). Patients with thin choroids had a higher prevalence of intra-/subretinal fluid (generalized estimated equation; thin versus medium  $p < 0.0001$ ; thin versus thick  $p = 0.003$ ), and less visual gain from baseline to 12 months after treatment, than did other subgroups (linear mixed model; thin versus medium  $p < 0.0001$ ; thin versus thick  $p = 0.023$ ). PCV eyes with thick choroids more often had retinal fluid, and eyes with thin choroids experienced more frequent resolution of retinal fluid, from baseline to 12 months after treatment (thick versus medium  $p < 0.0001$ , thick versus thin  $p < 0.0001$ , thin versus medium  $p = 0.001$ ). No intergroup difference in post-treatment functional outcome was noted in eyes with PCV ( $p = 0.584$ ).

**CONCLUSIONS:** Subfoveal choroidal thickness was associated with functional and anatomical outcomes after intravitreal ranibizumab injection in eyes with typical neovascular AMD and PCV.

PMID: 25581639 [PubMed - as supplied by publisher]

## **Drugs Today (Barc). 2014 Dec;50(12):779-90.**

### **Aflibercept: an update on recent milestones achieved.**

Palejwala NV, Lauer AK.

**Abstract:** In the last decade, intravitreal medications targeted to vascular endothelial growth factor (VEGF) such as pegaptanib, ranibizumab and bevacizumab have revolutionized the treatment and significantly improved visual acuity outcomes in patients with retinal vascular diseases such as age-related macular degeneration (AMD), diabetic macula edema (DME) and retinal vein occlusion (RVO). In recent years, aflibercept, an anti-VEGF drug that targets all isoforms of VEGF as well as placenta growth factor, has shown similar effectiveness in recent clinical trials. Aflibercept has firmly joined ranibizumab and bevacizumab as an important therapeutic option in the management of neovascular AMD. More recently, aflibercept

appears to be contending with ranibizumab and bevacizumab as an important therapeutic option in the management of DME and RVO.

PMID: 25588083 [PubMed - in process]

**J Ophthalmol. 2014;2014:595132. Epub 2014 Dec 21.**

**A delphi study to detect deficiencies and propose actions in real life treatment of neovascular age-related macular degeneration.**

García-Layana A, Arias L, Figueroa MS, Araiz J, Ruiz-Moreno JM, García-Arumí J, Gómez-Ulla F, López-Gálvez MI, Cabrera-López F, García-Campos JM, Monés J, Cervera E, Armadá F, Gallego-Pinazo R, Piñero-Bustamante A, Serrano-Garcia MA.

**Purpose:** Spanish retina specialists were surveyed in order to propose actions to decrease deficiencies in real-life neovascular age macular degeneration treatment (nv-AMD).

**Methods:** One hundred experts, members of the Spanish Vitreoretinal Society (SERV), were invited to complete an online survey of 52 statements about nv-AMD management with a modified Delphi methodology. Four rounds were performed using a 5-point Linkert scale. Recommendations were developed after analyzing the differences between the results and the SERV guidelines recommendations.

**Results:** Eighty-seven specialists completed all the Delphi rounds. Once major potential deficiencies in real-life nv-AMD treatment were identified, 15 recommendations were developed with a high level of agreement. Consensus statements to reduce the burden of the disease included the use of treat and extend regimen and to reduce the amount of diagnostic tests during the loading phase and training technical staff to perform these tests and reduce the time between relapse detection and reinjection, as well as establishing patient referral protocols to outside general ophthalmology clinics.

**Conclusion:** The level of agreement with the final recommendations for nv-AMD treatment among Spanish retinal specialist was high indicating that some actions could be applied in order to reduce the deficiencies in real-life nv-AMD treatment.

PMID: 25587438 [PubMed] PMCID: PMC4283441

**Ophthalmology. 2015 Jan 8. pii: S0161-6420(14)01013-6. doi: 10.1016/j.ophtha.2014.10.013. [Epub ahead of print]**

**Therapies for Macular Edema Associated with Central Retinal Vein Occlusion: A Report by the American Academy of Ophthalmology.**

Yeh S, Kim SJ, Ho AC, Schoenberger SD, Bakri SJ, Ehlers JP, Thorne JE.

**PURPOSE:** To review the available evidence regarding the safety and efficacy of therapies for the treatment of macular edema (ME) associated with central retinal vein occlusion (CRVO).

**METHODS:** A literature search of the PubMed database was last conducted in March 2014 with no date restrictions but limited to articles published in English. A literature search of the Cochrane Library was also conducted in March 2014 with no date restrictions and without a language limitation. The combined searches yielded 108 citations, of which 20 were deemed clinically relevant for the Ophthalmic Technology Assessment Committee Retina/Vitreous panel to review in full text. Three additional studies were also identified for panel review. The level of evidence of these selected studies was reviewed by the panel methodologist.

**RESULTS:** There were 7 citations representing 4 clinical trials that provided level I evidence supporting the use of anti-vascular endothelial growth factor (VEGF) pharmacotherapies for ME associated with CRVO, including intravitreal ranibizumab (2), aflibercept (3), and bevacizumab (2). There were 3 citations representing 2 studies with level I evidence for intravitreal corticosteroid injection with dexamethasone

intravitreal implant (2 citations) or triamcinolone (1 citation), although cataract and glaucoma were observed in these studies. Level I evidence is available on the limited benefit of macular grid-pattern laser photocoagulation (1 citation). Eight other citations reviewed were rated as level II, and 4 citations were rated as level III. Long-term efficacy results ( $\geq 2$  years of follow-up) are limited to intravitreal ranibizumab at this time, and few studies have evaluated combination therapy with anti-VEGF and corticosteroid versus monotherapy of either class of drug.

**CONCLUSIONS:** Level I evidence indicates that intravitreal anti-VEGF pharmacotherapy is safe and effective over 2 years for ME associated with CRVO and that delay in treatment is associated with worse visual outcomes. In addition, level I evidence demonstrates short-term efficacy of intravitreal corticosteroid but also an association with a higher frequency of adverse events.

PMID: 25576994 [PubMed - as supplied by publisher]

## **Ophthalmology. 2015 Jan 9. [Epub ahead of print]**

### **Pigment Epithelial Detachment Followed by Retinal Cystoid Degeneration Leads to Vision Loss in Treatment of Neovascular Age-Related Macular Degeneration.**

Schmidt-Erfurth U, Waldstein SM, Deak GG, Kundi M, Simader C.

**PURPOSE:** Intravitreal antiangiogenic therapy is the major therapeutic breakthrough in neovascular age-related macular degeneration (AMD). Optical coherence tomography (OCT) is the leading diagnostic tool, but solid criteria for optimal therapeutic outcomes are lacking. A comprehensive analysis of structure/function correlations using Food and Drug Administration- and European Medicines Agency-approved substances and fixed and flexible regimens was performed.

**DESIGN:** Post hoc analysis of a prospective, randomized multicenter clinical trial including 189 study sites.

**PARTICIPANTS:** A total of 1240 patients with active neovascular AMD.

**METHODS:** Participants received intravitreal ranibizumab or aflibercept. A fixed regimen was used for 48 weeks followed by a flexible regimen until week 96. At monthly intervals, best-corrected visual acuity (BCVA) was measured and retinal morphology was assessed by standardized OCT, including intraretinal cysts (IRCs), subretinal fluid (SRF), and pigment epithelial detachment (PED), presenting with a width  $\geq 400$   $\mu\text{m}$  or a height of  $\geq 200$   $\mu\text{m}$ . Results were correlated for each regimen, feature, and time.

**MAIN OUTCOME MEASURES:** The BCVA outcomes in relation to retinal pathomorphology based on noninferiority for all treatment arms.

**RESULTS:** In neovascular AMD, only IRC at baseline and persistent through week 12 had a negative impact on BCVA. With therapeutic intervention, exudative features such as IRC and SRF resolved rapidly in 74% of eyes, whereas PED responded only slowly with 38%. Independent of the type of regimen, fixed or flexible, retinal morphology correlated tightly with visual function. Intraretinal cysts consistently showed the lowest BCVA gains with either regimen or substance. With the switch from a fixed to a flexible pro re nata (PRN) regimen, progressive visual loss occurred exclusively in the group with primary PED presenting as the hallmark of neovascular activity and was induced by secondary formation of IRC in the neurosensory retina.

**CONCLUSIONS:** The efficacy of antiangiogenic therapy in neovascular AMD is strongly determined by morphologic features. The subretinal pigment epithelium lesion underlying PED appears to be the primary indicator for progressive disease activity, whereas secondary cystoid degeneration is the most relevant imaging marker for visual function. Clinically, PED emerged as trigger for consecutive vision loss in PRN treatment.

PMID: 25578255 [PubMed - as supplied by publisher]

**Retina. 2015 Jan 14. [Epub ahead of print]**

# **CHANGES OF CHOROIDAL NEOVASCULARIZATION IN INDOCYANINE GREEN ANGIOGRAPHY AFTER INTRAVITREAL RANIBIZUMAB INJECTION.**

Lee JE, Kim HW, Lee SJ, Lee JE.

**PURPOSE:** To investigate vascular structural changes of choroidal neovascularization (CNV) followed by intravitreal ranibizumab injections using indocyanine green angiography.

**METHODS:** A total of 31 patients with exudative age-related macular degeneration and CNV whose structures were identifiable in indocyanine green angiography were included. Ranibizumab was injected into the vitreous cavity once a month for 3 months and then as needed for the next 3 months prospectively. Indocyanine green angiography was performed at baseline, 3, and 6 months. Early to midphase images of the indocyanine green angiography in the details of vascular structure of the CNV were discerned the best were used in the image analysis. Vascular structures of CNV were described as arteriovenular and capillary components, and structural changes were assessed.

**RESULTS:** Arteriovenular components were observed in 29 eyes (94%). Regression of the capillary components was observed in most cases. Although regression of arteriovenular component was noted in 14 eyes (48%), complete resolution was not observed. The eyes were categorized into 3 groups according to CNV structural changes: the regressed (Group R, 10 eyes, 31%), the matured (Group M, 7 eyes, 23%), and the growing (Group G, 14 eyes, 45%). In Group R, there was no regrowth of CNV found at 6 months. In Group M, distinct vascular structures were observed at 3 months and persisted without apparent changes at 6 months. In Group G, growth or reperfusion of capillary components from the persisting arteriovenular components was noted at 6 months.

**CONCLUSION:** Both capillary and arteriovenular components were regressed during monthly ranibizumab injections. However, CNV regrowth was observed in a group of patients during the as-needed treatment phase.

PMID: 25590857 [PubMed - as supplied by publisher]

**Retina. 2015 Jan 8. [Epub ahead of print]**

# **INCIDENCE OF OUTER RETINAL TUBULATION IN RANIBIZUMAB-TREATED AGE-RELATED MACULAR DEGENERATION.**

Dirani A, Gianniou C, Marchionno L, Decugis D, Mantel I.

**PURPOSE:** To investigate the incidence of outer retinal tubulation (ORT) in ranibizumab-treated neovascular age-related macular degeneration patients.

**METHODS:** We included 480 consecutive patients (546 eyes) with neovascular age-related macular degeneration, who were treated with variable-dosing intravitreal ranibizumab, evaluated with spectral domain optical coherence tomography, and followed-up for a minimum period of 6 months. Optical coherence tomographies were evaluated for the first appearance of ORT, precursor signs, and type of underlying lesion. Visual acuity was also recorded.

**RESULTS:** Outer retinal tubulation was observed in 30% of eyes during a mean follow-up period of 26.7 months (SD, 13.5). Kaplan-Meier survival analysis revealed that the ORT incidence (2.5, 17.5, 28.4, and 41.6% at baseline, after 1, 2, and 4 years, respectively) continuously increased, despite visually effective anti-vascular endothelial growth factor treatment. Outer retinal tubulation was associated with a poorer functional benefit. Lower baseline visual acuity was associated with a higher risk of developing ORT.

**CONCLUSION:** Incidence of ORT continuously increases despite visually optimal anti-vascular endothelial growth factor treatment of age-related macular degeneration. Outer retinal tubulation might be considered a prognostic factor for functional outcome and is relevant to avoid overtreatment.

PMID: 25574786 [PubMed - as supplied by publisher]

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**Ophthalmologe. 2015 Jan 10. [Epub ahead of print]**

**[Laser treatment or intravitreal VEGF inhibition for aggressive posterior retinopathy of prematurity?] [Article in German]**

Barth T, Hufendiek K, Helbig H, Oberacher-Velten I.

**Abstract:** A prematurely born male infant (24+5 gestational weeks, birth weight 485 g) was diagnosed with bilateral aggressive posterior retinopathy of prematurity (AP-ROP) in zone I. After obtaining informed written consent from the parents, one eye was treated with diode laser photocoagulation and the other eye with 0.25 mg intravitreal ranibizumab. Laser photocoagulation was found to be an effective tool for fast regression of AP-ROP; however, medium-term evaluation showed poor macular formation and peripheral retinal detachment. The intravitreal injection led to a slower but better control of the AP-ROP and central foveal reflexes showed better anatomical outcome.

PMID: 25573085 [PubMed - as supplied by publisher]

**Ophthalmologica. 2014 Dec 24. [Epub ahead of print]**

**Comment on the Paper by Douvali et al. Entitled 'Effect of Macular Ischemia on Intravitreal Ranibizumab Treatment for Diabetic Macular Edema'**

Ilhan A, Tas A, Yolcu U, Gundogan FC.

PMID: 25573028 [PubMed - as supplied by publisher]

**Long-Term Use of Ranibizumab for the Treatment of Age-Related Macular Degeneration: A Review of the Clinical and Cost-Effectiveness and Guidelines**

**Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014 Mar.**

CADTH Rapid Response Reports.

Excerpt

The purpose of this review is to evaluate the clinical evidence, cost information, and guidelines to determine if there is evidence to support dosing regimens of 15 or more injections of ranibizumab for the treatment of age-related macular degeneration (AMD).

PMID: 25590116 [PubMed]

## Other treatment & diagnosis

**Invest Ophthalmol Vis Sci. 2015 Jan 13. [Epub ahead of print]**

**Choroidal Thickness in Geographic Atrophy secondary to Age- Related Macular Degeneration.**

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

**Purpose:** To analyze choroidal thickness (CT) in eyes with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) **Methods** A total of 72 eyes of 72 patients (mean age 75.97±7.09 years) with GA and 37 eyes of 37 healthy controls (73.89±6.19 years) were examined by confocal scanning-laser-ophthalmoscopy and enhanced depth imaging (EDI) spectral domain optical coherence tomography. CT was measured at 25 defined points in horizontal and vertical scans. GA size was determined in fundus-autofluorescence (FAF) images and GA subtypes were classified based on abnormal FAF in the

perilesional zone. Results In GA, subfoveal CT (fCT) was significantly thinner as compared to controls ( $173.03 \pm 90.22 \mu\text{m}$  vs.  $253.95 \pm 69.19 \mu\text{m}$ ,  $p < 0.001$ ). Analysis of averaged measurements of all 25 points obtained per patient (mCT) revealed similar results ( $162.07 \pm 76.26 \mu\text{m}$  vs.  $228.00 \pm 66.24 \mu\text{m}$ ,  $p < 0.001$ ). Spatial differences in CT between both groups were largest superior to the fovea. Addressing "diffuse-trickling" ( $n=15$ ) and "non-diffuse-trickling" ( $n=57$ ) GA independently, fCT was  $114.67 \pm 43.32 \mu\text{m}$  and  $188.39 \pm 93.26 \mu\text{m}$ , respectively ( $p=0.002$ ) both groups being significantly thinner than controls ( $p=0.001$  for "diffuse-trickling" and  $p < 0.001$  for "non-diffuse-trickling"). Similar results were obtained for mCT, which was  $110.21 \pm 29.66 \mu\text{m}$  in "diffuse-trickling",  $175.72 \pm 79.02 \mu\text{m}$  in "non-diffuse-trickling" and  $228.00 \pm 66.24 \mu\text{m}$  in controls. Differences were significant with  $p=0.002$  between both GA groups and  $p \leq 0.001$  towards controls for each GA group. Conclusions The results indicate that the choroid in eyes with GA is thinner compared to normal eyes of similar age. Hereby, the extent of thinning is most pronounced in a specific subtype of GA identified by FAF imaging ("diffuse trickling"). Such GA-subtype related differences in choroidal thickness may reflect heterogeneity in the pathogenesis of disease.

PMID: 25587059 [PubMed - as supplied by publisher]

### **Br J Ophthalmol. 2015 Jan 13. [Epub ahead of print]**

#### **MultiColor imaging in the evaluation of geographic atrophy due to age-related macular degeneration.**

Moussa NB, Georges A, Capuano V, Merle B, Souied EH, Querques G.

**PURPOSE:** To compare different imaging modalities and to investigate the ability of MultiColor to evaluate geographic atrophy (GA) due to age-related macular degeneration (AMD).

**METHODS:** Twenty-two consecutive patients with GA underwent MultiColor, colour fundus photography, blue fundus autofluorescence (FAF) (excitation=488 nm; emission >500 nm), near-infrared FAF (NIR-FAF) (excitation=787 nm; emission >800 nm) and spectral-domain optical coherence tomography (SD-OCT) (Spectralis HRA+OCT; Heidelberg Engineering) imaging. Two readers independently measured the size (area) and the width of GA (on horizontal SD-OCT scan cutting the fovea), and evaluated the foveal sparing in each examination.

**RESULTS:** A total of 32 eyes (22 patients, mean age  $79.2 \pm 8$  years) with GA were included. Intra-grader and inter-grader agreement considering the evaluation of the size and width of GA was high for all the examinations. MultiColor and FAF showed the greatest inter-grader agreement for GA area measurement (intraclass correlation (ICC)=0.990, 95% CI 0.980 to 0.995; ICC=0.998, 95% CI 0.996 to 0.999, respectively). SD-OCT showed the highest inter-grader agreement of foveal involvement ( $k=1$ ), followed by MultiColor and NIR-FAF ( $k=0.68$ ).

**CONCLUSIONS:** We demonstrated that several different imaging modalities currently available in clinical practice are reliable for evaluating GA due to AMD. MultiColor is an excellent tool for the measurement of GA area and width, and for the detection of foveal sparing.

PMID: 25586715 [PubMed - as supplied by publisher]

### **Acta Ophthalmol. 2015 Jan 13. [Epub ahead of print]**

#### **Nutritional supplements in age-related macular degeneration.**

Schmidl D, Garhöfer G, Schmetterer L.

**Abstract:** Age-related macular degeneration (AMD) is the most frequent cause of blindness in the Western World. While with new therapies that are directed towards vascular endothelial growth factor (VEGF), a potentially efficient treatment option for the wet form of the disease has been introduced, a therapeutic regimen for dry AMD is still lacking. There is evidence from several studies that oral intake of supplements is beneficial in preventing progression of the disease. Several formulations of micronutrients are currently

available. The present review focuses on the role of supplements in the treatment and prevention of AMD and sums up the current knowledge about the most frequently used micronutrients. In addition, regulatory issues are discussed, and future directions for the role of supplementation in AMD are highlighted.

PMID: 25586104 [PubMed - as supplied by publisher]

## **J Med Chem. 2015 Jan 15. [Epub ahead of print]**

### **Stemistry: The Control of Stem Cells in Situ Using Chemistry.**

Davies SG, Kennewell PD, Russell AJ, Seden PT, Westwood R, Wynne GM.

**Abstract:** A new paradigm for drug research has emerged, namely the deliberate search for molecules able to selectively affect the proliferation, differentiation, and migration of adult stem cells within the tissues in which they exist. Recently, there has been significant interest in medicinal chemistry toward the discovery and design of low molecular weight molecules that affect stem cells and thus have novel therapeutic activity. We believe that a successful agent from such a discover program would have profound effects on the treatment of many long-term degenerative disorders. Among these conditions are examples such as cardiovascular decay, neurological disorders including Alzheimer's disease, and macular degeneration, all of which have significant unmet medical needs. This perspective will review evidence from the literature that indicates that discovery of such agents is achievable and represents a worthwhile pursuit for the skills of the medicinal chemist.

PMID: 25590360 [PubMed - as supplied by publisher]

## **Stem Cells Transl Med. 2015 Jan 15. [Epub ahead of print]**

### **Defined Culture of Human Embryonic Stem Cells and Xeno-Free Derivation of Retinal Pigmented Epithelial Cells on a Novel, Synthetic Substrate.**

Pennington BO, Clegg DO, Melkounian ZK, Hikita ST.

**Abstract:** Age-related macular degeneration (AMD), a leading cause of blindness, is characterized by the death of the retinal pigmented epithelium (RPE), which is a monolayer posterior to the retina that supports the photoreceptors. Human embryonic stem cells (hESCs) can generate an unlimited source of RPE for cellular therapies, and clinical trials have been initiated. However, protocols for RPE derivation using defined conditions free of nonhuman derivatives (xeno-free) are preferred for clinical translation. This avoids exposing AMD patients to animal-derived products, which could incite an immune response. In this study, we investigated the maintenance of hESCs and their differentiation into RPE using Synthemax II-SC, which is a novel, synthetic animal-derived component-free, RGD peptide-containing copolymer compliant with good manufacturing practices designed for xeno-free stem cell culture. Cells on Synthemax II-SC were compared with cultures grown with xenogeneic and xeno-free control substrates. This report demonstrates that Synthemax II-SC supports long-term culture of H9 and H14 hESC lines and permits efficient differentiation of hESCs into functional RPE. Expression of RPE-specific markers was assessed by flow cytometry, quantitative polymerase chain reaction, and immunocytochemistry, and RPE function was determined by phagocytosis of rod outer segments and secretion of pigment epithelium-derived factor. Both hESCs and hESC-RPE maintained normal karyotypes after long-term culture on Synthemax II-SC. Furthermore, RPE generated on Synthemax II-SC are functional when seeded onto parylene-C scaffolds designed for clinical use. These experiments suggest that Synthemax II-SC is a suitable, defined substrate for hESC culture and the xeno-free derivation of RPE for cellular therapies.

PMID: 25593208 [PubMed - as supplied by publisher]

## Pathogenesis

J Clin Med. 2014;3(4):1542-1560.

### **Inflammation and Cell Death in Age-Related Macular Degeneration: An Immunopathological and Ultrastructural Model.**

Ardeljan CP, Ardeljan D, Abu-Asab M, Chan CC.

**Abstract:** The etiology of Age-related Macular Degeneration (AMD) remains elusive despite the characterization of many factors contributing to the disease in its late-stage phenotypes. AMD features an immune system in flux, as shown by changes in macrophage polarization with age, expression of cytokines and complement, microglial accumulation with age, etc. These point to an allostatic overload, possibly due to a breakdown in self vs. non-self when endogenous compounds and structures acquire the appearance of non-self over time. The result is inflammation and inflammation-mediated cell death. While it is clear that these processes ultimately result in degeneration of retinal pigment epithelium and photoreceptor, the prevalent type of cell death contributing to the various phenotypes is unknown. Both molecular studies as well as ultrastructural pathology suggest pyroptosis, and perhaps necroptosis, are the predominant mechanisms of cell death at play, with only minimal evidence for apoptosis. Herein, we attempt to reconcile those factors identified by experimental AMD models and integrate these data with pathology observed under the electron microscope-particularly observations of mitochondrial dysfunction, DNA leakage, autophagy, and cell death.

PMID: 25580276 [PubMed] PMCID: PMC4287551

**Exp Eye Res. 2015 Jan 7. [Epub ahead of print]**

### **Blue light-induced inflammatory marker expression in the retinal pigment epithelium-choroid of mice and the protective effect of a yellow intraocular lens material in vivo.**

Narimatsu T, Negishi K, Miyake S, Hirasawa M, Kurihara T, Tsubota K, Ozawa Y.

**Abstract:** Oxidative stress in the retinal pigment epithelium (RPE) is a well-accepted pathogenic change in vision-threatening diseases such as age-related macular degeneration. One source of oxidative stress is excessive light exposure, which causes excessive activation of the visual cycle. Because short wavelength light (blue light) has more energy, it is reported to be more harmful to photoreceptor cells than the other wavelengths of light. However, the biological effect of blue light in the RPE of living animals and the protective effect of a yellow intraocular lens (IOL) material that blocks blue light is still obscure. Therefore, we compared the pathogenic effect in the RPE-choroid complexes of mice exposed to light in a box made of a clear or a yellow IOL material. We measured the level of reactive oxygen species (ROS) using 2', 7'-dichlorodihydrofluorescein diacetate, the mRNA levels of inflammatory cytokines and a macrophage marker by real-time polymerase chain reaction, and the protein levels of monocyte chemotactic protein-1 (MCP-1) and macrophage markers by ELISA. The ROS level after light exposure was suppressed in the RPE-choroids of light-exposed mice in the yellow IOL material box. In parallel, all the inflammatory cytokines that we measured and a macrophage marker were also suppressed in the RPE-choroids of light-exposed mice in the yellow IOL material box. Therefore, a yellow IOL material suppressed, and thus blue light exacerbated, the increase in the ROS level and inflammatory cytokine expression as well as macrophage recruitment in the RPE-choroid in vivo after light exposure.

PMID: 25576667 [PubMed - as supplied by publisher]

**Exp Eye Res. 2015 Jan 7;131C:77-83.[Epub ahead of print]**

### **Excessive retinol intake exacerbates choroidal neovascularization through upregulated vascular endothelial growth factor in retinal pigment epithelium in mice.**

Tan X, Takahashi H, Nishida J, Aoki A, Inoue T, Yanagi Y.

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**Abstract:** As a part of the visual cycle, all-trans-retinol (all-trans-ROL), the major form of vitamin A in circulating blood, is transported to the retinal pigment epithelium (RPE). All-trans-ROL is essential for normal retina function. However, recent researches have shown that excessive retinol intake can cause increase of all-trans-retinal. This can lead to the accumulation of lipofuscin, which is important in the pathogenesis of retina degeneration disease, such as dry type age-related macular degeneration (AMD). Since there are few reports regarding the involvement of all-trans-ROL in exudative AMD, we investigated the effects of all-trans-ROL in vitro and in vivo. We evaluated vascular endothelial growth factor (VEGF) expression in ARPE-19 cells and THP-1 cells after all-trans-ROL treatment using ELISA and real-time RT-PCR. In-vitro tube formation assay was performed with HUVEC cells using the conditioned medium (CM) obtained from ARPE-19 cells treated with all-trans-ROL. Transcriptional activity of retinoic acid receptor (RAR) was evaluated using luciferase assay. In mice, VEGF expressions were investigated in the retina and RPE/choroid after three weeks of excessive oral retinol intake. Laser-induced choroidal neovascularization (CNV) models were evaluated after they were fed with various doses of retinol. VEGF mRNA expression and VEGF production were significantly increased in all-trans-ROL treated ARPE-19 cells, which were inhibited by an RAR antagonist LE540. In contrast, there were no significant changes in VEGF production in THP-1 cells. Transcriptional activity of RAR was upregulated by all-trans-ROL treatment in ARPE-19 cells. The CM, obtained from ARPE-19 cells treated with all-trans-ROL, induced more capillary-like tube formation than cells treated with control vehicles. In vivo, the high retinol diet group has increased VEGF expression in the RPE/choroid and larger lesion size was induced. Our results suggest that all-trans-ROL is a pro-angiogenic factor. Excessive retinoid intake may be a potential risk factor for exudative AMD.

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**Sci Rep. 2015 Jan 9;5:7705.**

**Plasma-activated medium suppresses choroidal neovascularization in mice: a new therapeutic concept for age-related macular degeneration.**

Ye F, Kaneko H, Nagasaka Y, Ijima R, Nakamura K, Nagaya M, Takayama K, Kajiyama H, Senga T, Tanaka H, Mizuno M, Kikkawa F, Hori M, Terasaki H.

**Abstract:** Choroidal neovascularization (CNV) is the main pathogenesis of age-related macular degeneration (AMD), which leads to severe vision loss in many aged patients in most advanced country. CNV compromises vision via hemorrhage and retinal detachment on account of pathological neovascularization penetrating the retina. Plasma medicine represents the medical application of ionized gas "plasma" that is typically studied in the field of physical science. Here we examined the therapeutic ability of plasma-activated medium (PAM) to suppress CNV. The effect of PAM on vascularization was assessed on the basis of human retinal endothelial cell (HREC) tube formation. In mice, laser photocoagulation was performed to induce CNV (laser-CNV), followed by intravitreal injection of PAM. N-Acetylcysteine was used to examine the role of reactive oxygen species in PAM-induced CNV suppression. Fundus imaging, retinal histology examination, and electroretinography (ERG) were also performed to evaluate PAM-induced retinal toxicity. Interestingly, HREC tube formation and laser-CNV were both reduced by treatment with PAM. N-acetylcysteine only partly neutralized the PAM-induced reduction in laser-CNV. In addition, PAM injection had no effect on regular retinal vessels, nor did it show retinal toxicity in vivo. Our findings indicate the potential of PAM as a novel therapeutic agent for suppressing CNV.

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**Invest Ophthalmol Vis Sci. 2015 Jan 15. [Epub ahead of print]**

**Local production of the alternative pathway component, Factor B, is sufficient to promote laser-induced choroidal neovascularization.**

Schnabolk G, Coughlin B, Joseph K, Kunchithapautham K, Bandyopadhyay M, O'Quinn E, Nowling T, Rohrer B.

**Purpose:** Complement factor B (CFB) is a required component of the alternative pathway (AP) of complement; and CFB polymorphisms are associated with age-related macular degeneration (AMD) risk. CFB is made in the liver, but expression has also been detected in retina and retinal pigment epithelium (RPE)-choroid. We investigated whether production of CFB by the RPE can promote AP activation in mouse choroidal neovascularization (CNV).

**Methods:** Transgenic mice expressing CFB under the RPE65 promoter were generated and crossed onto factor-B-deficient (CFB-KO) mice. Biological activity was determined in vitro using RPE monolayers, and in vivo using laser-induced CNV. Contribution of systemic CFB was investigated using CFB-KO reconstituted with CFB-sufficient serum.

**Results:** Transgenic mice (CFB-tg) express CFB in RPE-choroid; no CFB was detected in serum. Cultured CFB-tg RPE monolayers secrete CFB apically and basally upon exposure to oxidative stress that was biologically active. CNV sizes were comparable between wild type and CFB-tg mice, but significantly increased when compared to lesions in CFB-KO mice. Injections of CFB-sufficient serum into CFB-KO mice resulted in partial reconstitution of systemic AP activity and significantly increased CNV size.

**Conclusions:** Mouse RPE cells express and secrete CFB sufficient to promote RPE damage and CNV. This further supports that local complement production may regulate disease processes; however, the reconstitution experiments suggest that additional components may be sequestered from the bloodstream. Understanding the process of ocular complement production and regulation will further our understanding of the AMD disease process and the requirements of a complement-based therapeutic.

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#### **Invest Ophthalmol Vis Sci. 2015 Jan 15. [Epub ahead of print]**

#### **Involvement of Intracellular Calcium Mobilization in IL-8 Activation in Human Retinal Pigment Epithelial Cells.**

Yang IH, Wong JH, Chang CM, Chen BK, Tsai YT, Chen WC, Wang ET, Hsu WL, Chang WC.

**PURPOSE:** Calcium signaling is an important intracellular pathway. Increased intracellular calcium is associated with cytokine regulation and inflammatory signals secretion. The purpose of this study is to understand the molecular mechanisms by which calcium signaling controls interleukin-8 (IL-8) activation in human retinal pigment epithelial (RPE) cells.

**METHODS:** Both fluorescence based calcium imaging and different mutants of IL-8 plasmids were used in this study. IL-8 promoter activation, gene expression and secretion were detected by using luciferase reporter assay, quantitative real-time polymerase chain reaction (Q-PCR) and enzyme-linked immunosorbent assay (ELISA), respectively. In addition, pharmacological inhibitors and small interfering RNA (siRNA) were applied to clarify the mechanisms of IL-8 activation.

**RESULTS:** Our study reported that intracellular calcium mobilization activated IL-8 gene expression and secretion. Application of pharmacological inhibitor BAY 11-7082, siRNA and plasmids of the mutated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) binding site, we further indicated that NF-κB is the main transcription factor involved in intracellular calcium mobilization-mediated IL-8 activation in human RPE cells.

**CONCLUSIONS:** Collectively, our findings highlight the important role of intracellular calcium mobilization in the activation of IL-8. These findings may be helpful for the clinical applications in the age-related macular degeneration (AMD) prevention and treatment.

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## Epidemiology

**Eye (Lond). 2015 Jan 16. [Epub ahead of print]**

### **Prevalence and incidence of blindness and other degrees of sight impairment in patients treated for neovascular age-related macular degeneration in a well-defined region of the United Kingdom.**

Buckle M, Lee A, Mohamed Q, Fletcher E, Sallam A, Healy R, Stratton I, Tufail A, Johnston RL.

**Aims:** This study aimed to evaluate the incidence and prevalence of blindness, sight impairment, and other visual acuity (VA) states in patients receiving ranibizumab for neovascular age-related macular degeneration (nAMD) in Gloucestershire.

**Methods:** Serial VA and injection data for all treatment-naïve patients receiving their first intravitreal injections of ranibizumab for nAMD in the Gloucestershire National Health Service Ophthalmology department between 2008 and 2010 were extracted from an electronic medical record system.

**Results:** The prevalence of blindness (VA in the better-seeing eye  $\leq 25$  Early Treatment Diabetic Retinopathy Study (ETDRS) letters) at the time of first intravitreal injection was 0.8%, increasing to 3.5% after 3 years. The prevalence of sight impairment (VA in the better-seeing eye 26-39 ETDRS letters) increased from 4.1% at baseline to 5.5% after 3 years. The incidence of initiating ranibizumab treatment for nAMD in people aged  $\geq 50$  years in Gloucestershire was 111 people per 100 000 population in 2009, and 97 people in 2010. The incidence of patients meeting the visual criteria for blindness and sight impairment registration from treated nAMD in people aged  $\geq 50$  years in Gloucestershire was 3.5 and 9.7 people, respectively per 100 000 population in 2010.

**Conclusion:** This is the first real-world study on the incidence and prevalence of eligibility for blindness and sight impairment registration in treated nAMD in the UK based on VA data. The incidence and prevalence of eligibility for certification of blindness or sight impairment in patients treated with ranibizumab for nAMD is low in Gloucestershire, with only 3.6% of the incident population progressing to blindness in 2010.

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**Int J Cardiol. 2014 Dec 30;182C:213-215. [Epub ahead of print]**

### **Relationship between macular degeneration with prevalent heart failure: A cross-sectional population study.**

Phan K, Mitchell P, Liew G, Plant AJ, Wang SB, Chiha J, Thiagalingam A, Burlutsky G, Gopinath B.

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## Genetics

**Pac Symp Biocomput. 2015;20:243-54.**

### **Mitochondrial variation and the risk of age-related macular degeneration across diverse populations.**

Restrepo NA, Mitchell SL, Goodloe RJ, Murdock DG, Haines JL, Crawford DC.

**Abstract:** Substantial progress has been made in identifying susceptibility variants for age-related macular degeneration (AMD). The majority of research to identify genetic variants associated with AMD has focused on nuclear genetic variation. While there is some evidence that mitochondrial genetic variation contributes to AMD susceptibility, to date, these studies have been limited to populations of European descent resulting in a lack of data in diverse populations. A major goal of the Epidemiologic Architecture for Genes Linked to Environment (EAGLE) study is to describe the underlying genetic architecture of common, complex

diseases across diverse populations. This present study sought to determine if mitochondrial genetic variation influences risk of AMD across diverse populations. We performed a genetic association study to investigate the contribution of mitochondrial DNA variation to AMD risk. We accessed samples from the National Health and Nutrition Examination Surveys, a U.S population-based, cross-sectional survey collected without regard to health status. AMD cases and controls were selected from the Third NHANES and NHANES 2007-2008 datasets which include non-Hispanic whites, non-Hispanic blacks, and Mexican Americans. AMD cases were defined as those > 60 years of age with early/late AMD, as determined by fundus photography. Targeted genotyping was performed for 63 mitochondrial SNPs and participants were then classified into mitochondrial haplogroups. We used logistic regression assuming a dominant genetic model adjusting for age, sex, body mass index, and smoking status (ever vs. never). Regressions and meta-analyses were performed for individual SNPs and mitochondrial haplogroups J, T, and U. We identified five SNPs associated with AMD in Mexican Americans at  $p < 0.05$ , including three located in the control region (mt16111, mt16362, and mt16319), one in MT-RNR2 (mt1736), and one in MT-ND4 (mt12007). No mitochondrial variant or haplogroup was significantly associated in non-Hispanic blacks or non-Hispanic whites in the final meta-analysis. This study provides further evidence that mitochondrial variation plays a role in susceptibility to AMD and contributes to the knowledge of the genetic architecture of AMD in Mexican Americans.

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## Diet & lifestyle

**Acta Ophthalmol. 2015 Jan 14. doi: 10.1111/aos.12478. [Epub ahead of print]**

**Increased risk of depressive disorder following a diagnosis of neovascular age-related macular degeneration.**

Chung SD, Ho J, Hwa P, Lee HC, Lin HC.

PMID: 25588712 [PubMed - as supplied by publisher]

**Invest Ophthalmol Vis Sci. 2014 Dec 18;56(1):403-11. doi: 10.1167/iovs.14-15581.**

**Antioxidative capacity of a dietary supplement on retinal hemodynamic function in a human lipopolysaccharide (LPS) model.**

Told R, Schmidl D, Palkovits S, Boltz A, Gouya G, Wolzt M, Witkowska KJ, Popa-Cherecheanu A, Werkmeister RM, Garhöfer G, Schmetterer L.

**PURPOSE:** Beneficial effects of dietary supplements in age-related macular degeneration (AMD) are related to antioxidative properties. In the Age-Related Eye Disease Study 1 (AREDS 1), a reduced progression to late stage AMD was found using vitamin C, E, zinc, and  $\beta$ -carotene. We showed previously that the AREDS 1 formulation restores the O<sub>2</sub>-induced retinal vasoconstrictor response of retinal vessels in a human endotoxin (lipopolysaccharide [LPS]) model.

**METHODS:** We hypothesized that the abnormal O<sub>2</sub>-induced retinal red blood cell (RBC) flow response can be modulated by a different formulation (vitamin C, E, and zinc, lutein/zeaxanthin, selenium, taurine, Aronia extract, and omega-3 free fatty acids). A total of 43 healthy subjects was included in this randomized, double masked, placebo-controlled parallel group study. The reactivity of retinal arterial and venous diameter, RBC velocity, and flow to 100% O<sub>2</sub> breathing was investigated in the absence and presence of 2 ng/kg LPS. Between the two study days was a 14-day period of daily dietary supplement intake.

**RESULTS:** The decrease in retinal arterial diameter, RBC velocity, and flow during 100% O<sub>2</sub> breathing was diminished significantly after LPS infusion. Dietary supplement intake for 14 days almost restored the response of retinal hemodynamic parameters to 100% O<sub>2</sub> after LPS administration. This effect was significant for retinal arterial diameter ( $P = 0.03$  between groups), and RBC velocity and flow (each  $P < 0.01$ ).

between groups).

**CONCLUSIONS:** The present data indicate restoring of the RBC flow response to 100% O<sub>2</sub> after LPS administration. This is likely due to an amelioration of endothelial dysfunction resulting from oxidative stress, a factor involved in AMD pathophysiology. (ClinicalTrials.gov number, NCT00914576.).

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