

Issue 303

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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

**Eur J Ophthalmol. 2016 Oct 27:0. [Epub ahead of print]**

**One-year results of aflibercept in vascularized pigment epithelium detachment due to neovascular AMD: a prospective study.**

Veritti D, Sarao V, Parravano M, Arias L, Varano M, Lanzetta P.

**PURPOSE:** To evaluate individualized intravitreal aflibercept regimens for treatment of neovascular age-related macular degeneration (nAMD)-related pigment epithelial detachment (PED).

**METHODS:** This prospective, multicenter, nonrandomized study included 32 eyes with nAMD-related PED, treated with ranibizumab for  $\geq 6$  months. All patients received intravitreal aflibercept (2 mg/0.05 mL) at baseline (no loading phase) and subsequently treated pro re nata with monthly follow-up for 12 months. Outcome measures included visual acuity, central retinal thickness (CRT), PED height and area, and neovascular network size.

**RESULTS:** At 12 months, aflibercept improved mean best-corrected visual acuity compared with baseline values ( $p < 0.05$ ); 50% of patients displayed complete resolution of intraretinal and/or subretinal fluid. Compared with baseline, significant decreases were observed for mean CRT and PED height (both  $p < 0.01$ ).

**CONCLUSIONS:** Aflibercept appears to induce anatomical improvement for at least 12 months after conversion from ranibizumab in patients experiencing nAMD-related PED. Significant reductions in both mean PED height and CRT were observed, although these changes were not necessarily related to significantly improved visual acuity scores. However, larger patient cohorts are required to extend and validate our results, and increased study duration would allow exploration of the potential long-term benefits and challenges of prolonged aflibercept use.

PMID: 27791249

**Pharmacoeconomics. 2016 Oct 27. [Epub ahead of print]**

**Simulation Modelling in Ophthalmology: Application to Cost Effectiveness of Ranibizumab and Aflibercept for the Treatment of Wet Age-Related Macular Degeneration in the United Kingdom.**

Claxton L, Hodgson R, Taylor M, Malcolm B, Pulikottil Jacob R.

**BACKGROUND:** Previously developed models in ophthalmology have generally used a Markovian structure. There are a number of limitations with this approach, most notably the ability to base patient outcomes on best-corrected visual acuity (BCVA) in both eyes, which may be overcome using a different modelling structure. Simulation modelling allows for this to be modelled more precisely, and therefore may provide more accurate and relevant estimates of the cost effectiveness of ophthalmology interventions.

**OBJECTIVE:** This study aimed to explore the appropriateness of simulation modelling in ophthalmology, using the disease area of wet age-related macular degeneration (wAMD) as an example.

**METHODS:** A de novo economic model was built using a patient-level simulation, which compared ranibizumab with aflibercept in wAMD. Disease progression was measured using BCVA. Health-related quality of life (HRQoL) was estimated using a regression analysis linking BCVA in each eye to utility. The analysis was from the perspective of the National Health Service in the UK. Five different regression models were explored and were based on BCVA in either one eye or both eyes.

**RESULTS:** The model outputs provide some evidence to support the hypothesis that the analyses using the two-eye models for estimating HRQoL generate a more accurate estimation of incremental quality-adjusted life-years (QALYs) associated with the positive treatment effect for ranibizumab versus aflibercept. Second-order analysis broadly supported these findings, and showed that the variation in incremental costs was slightly lower than in incremental QALYs. The second-order analysis estimated similar incremental costs and a greater overall variation in incremental QALYs than the first-order analysis, suggesting important non-linearities within the model.

**CONCLUSIONS:** This analysis suggests that patient-level simulation models may be well suited to representing the real-world patient pathway in wAMD, particularly when aspects of disease progression cannot be adequately captured using a Markov structure. The benefits of a simulation approach can be demonstrated in the modelling of HRQoL as a function of BCVA in both eyes.

PMID: 27787744

### **Case Rep Ophthalmol. 2016 Sep 26;7(3):162-171.**

#### **Long-Term Management of Complications of Retinal Artery Macroaneurysms with Intravitreal Aflibercept Injection.**

Kishore K.

**PURPOSE:** To report the 1-year follow-up results of intravitreal aflibercept injection (IAI) for the management of complications of retinal artery macroaneurysms (RAM).

**METHODS:** A retrospective, noncomparative, interventional case series of 4 eyes of 4 patients (all female, aged 68-91 years, 3 treatment naive) treated with IAI 2 mg for complications of RAM [macular edema (ME) 2, submacular hemorrhage (SMH) 1, and vitreous hemorrhage (VH) 1] was conducted. Baseline parameters consisted of complete ocular examination, medical history, best-corrected Snellen VA, fundus photography, IVFA and SD OCT, unless precluded by VH (1). All patients completed  $\geq 1$  year follow-up.

**RESULTS:** Baseline VA was hand motions in the eye with SMH (31 mm<sup>2</sup> area and 1,478  $\mu$ m thickness); 20/40 and 20/100 with ME (CST 390 and 337  $\mu$ m, respectively), and 20/200 in the eye with VH. At 1 month, both patients with ME showed resolution of ME with CST  $<300$   $\mu$ m with improvement in VA which was maintained through 1 year. VH resolved in one eye at 1 month with no recurrence after 1 year. The eye with SMH developed macular scar and had counting fingers vision at 1 year. Thrombosis of RAM was noted in all eyes and hairpin-like remodeling of artery in one. No eye required repeat injection or laser.

**CONCLUSION:** ME and VH from RAM were effectively treated with IAI. However, the eye with thick SMH had poor visual outcome despite thrombosis of RAM. Single IAI provided effective therapy for complications of RAM with excellent anatomical and visual results in each eye, except one with thick SMH, and merits further study.

PMID: 27790133

**J Fr Ophtalmol. 2016 Oct 24. [Epub ahead of print]**

**[Management algorithm of age-related macular degeneration with aflibercept: Real-life application].  
[Article in French]**

Gualino V, Baillif S, Kodjikian L.

**Abstract:** Aflibercept is indicated in France for wet age-related macular degeneration (wAMD) since November 2013. Its official dosage consists in administering one monthly intravitreal injection (IVT) during three months followed by one control visit and one IVT every two months the first year. In 2015, a group of French ophthalmologists, specialized in wAMD management, established a therapeutic algorithm to optimize naive patient management with aflibercept in order to obtain visual acuity gain. It indicates that official administration scheme is adapted for 80% of patients and that an adaptation of therapeutic scheme is needed for others. These experts recommended mostly the use of personalized proactive administration scheme. Since, aflibercept clinical use has significantly grown with interventional observational studies which results are now available. Use of aflibercept and of personalized proactive administration schemes allow in real-life obtaining important visual acuity gain, which is consistent with the established algorithm.

PMID: 27789040

**Retina. 2016 Oct 26. [Epub ahead of print]**

**INCIDENCE AND CAUSES OF VISION LOSS DURING AFLIBERCEPT TREATMENT FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: One-Year Follow-up.**

Hata M, Oishi A, Yamashiro K, Ooto S, Tamura H, Nakanishi H, Ueda-Arakawa N, Akagi-Kurashige Y, Kuroda Y, Takahashi A, Tsujikawa A, Yoshimura N.

**PURPOSE:** To investigate the incidence rate, risk factors, and final outcomes of patients with age-related macular degeneration (AMD) who have experienced vision loss despite periodic aflibercept treatment.

**METHODS:** Subjects with treatment-naïve AMD were prospectively recruited and treated with three monthly injections followed by two monthly injections of aflibercept. The incidence rate and risk factors of more than two lines of vision loss at any visit were investigated.

**RESULTS:** We included 196 eyes of 196 patients. Vision loss was observed in 16 patients (8.2%). Eleven of 16 patients developed vision loss during the initial 3 months (68.8%). Vision loss remained in 11 eyes (68.8%) at the final visit. The maximum pigment epithelium detachment (PED) height (odds ratio = 1.46 for a 100-μm increase in the PED height) and disruption of the external limiting membrane (odds ratio = 4.45) were identified as risk factors for developing vision loss on logistic regression analysis.

**CONCLUSION:** The incidence rate of vision loss during aflibercept treatment was relatively low. Identifying high-risk patients, those with a high PED height and disruption of the external limiting membrane, would be helpful in ensuring appropriate informed consent before treatment. Further studies are needed to establish optimal treatment for these patients.

PMID: 27787445

**Retina. 2016 Oct 26. [Epub ahead of print]**

**COMBINED INTRAVITREAL RANIBIZUMAB AND ORAL SUPPLEMENTATION WITH DOCOSAHEXAENOIC ACID AND ANTIOXIDANTS FOR DIABETIC MACULAR EDEMA: Two-Year Randomized Single-Blind Controlled Trial Results.**

Lafuente M, Ortín L, Argente M, Guindo JL, López-Bernal MD, López-Román FJ, García MJ, Domingo JC, Lajara J.

**PURPOSE:** To assess the 2-year effectiveness of intravitreal ranibizumab combined with a dietary supplement rich in docosahexaenoic acid (DHA) plus antioxidants in 62 patients with diabetic macular edema.

**METHODS:** In a randomized single-blind controlled study, 33 subjects (42 eyes) received intravitreal ranibizumab alone and 29 (34 eyes) combined with DHA (1,050 mg/day). Monthly ranibizumab (0.5 mg) was given for the first 4 months followed by on as-needed treatment.

**RESULTS:** At 24 months, the difference between groups in the decrease of central subfield macular thickness was significant in favor of the DHA supplementation group (95% confidence interval of the difference 7.20-97.656;  $P = 0.024$ ), although improvement in best-corrected visual acuity measured in the Early Treatment Diabetic Retinopathy Study letters did not reach statistical significance (95% confidence interval 5.4-11.2,  $P < 0.66$ ). At 24 months, gains of  $>5$  and  $>10$  letters were significantly higher in the DHA supplementation group as compared with controls when the worse and better seeing eyes were considered but other differences at 12 months and 24 months were not found.

**CONCLUSION:** Intravitreal ranibizumab combined with DHA supplementation reduced central subfield macular thickness after 2 years of follow-up as compared with ranibizumab alone in patients with diabetic macular edema. This anatomical improvement was accompanied by a trend for an amelioration of vision. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

PMID: 27787443

**Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5688-5695.**

**Optic Nerve Head Biomechanic and IOP Changes Before and After the Injection of Aflibercept for Neovascular Age-Related Macular Degeneration.**

Rebolleda G, Puerto B, de Juan V, Gómez-Mariscal M, Muñoz-Negrete FJ, Casado A.

**PURPOSE:** We investigated the early effects of intravitreal aflibercept injection (IAI) on optic nerve head (ONH) morphology.

**METHODS:** All of the participants underwent applanation tonometry and enhanced depth imaging by spectral-domain optical coherence tomography immediately before injection, and within 5 and 30 minutes after IAI. Changes in the anterior lamina cribrosa surface depth, prelaminar tissue thickness (PTT), optic cup width, optic cup depth, and Bruch's membrane opening (BMO) were assessed.

**RESULTS:** The study included 30 eyes of 30 subjects with a mean age of  $77.4 \pm 6.8$  years (range, 65-89 years) following IAI (2 mg in 0.05 ml). Within 5 minutes after injection, the mean cup depth, mean cup width, and BMO were significantly increased ( $P = 0.013$ ,  $P = 0.000$ , and  $P = 0.004$ , respectively), whereas the mean PTT was thinned ( $P = 0.009$ ). These morphologic changes returned to near baseline values 30 minutes after injection. Cup widening and BMO expansion ( $P = 0.000$ ;  $r, 0.668$ ), as well as cup deepening and prelaminar thinning ( $P = 0.000$ ;  $r, -0.838$ ), were significantly correlated. The magnitude of cup deepening and prelaminar tissue thinning correlated with the IOP change in the opposite direction than expected ( $P = 0.039$ ;  $r, -0.379$  and  $P = 0.377$ ;  $r, 0.040$ ).

**CONCLUSIONS:** A significant widening and deepening of the optic cup, BMO expansion, and prelaminar tissue thinning occurred following IAI for neovascular AMD. Eyes having greater optic disc cup deepening and prelaminar tissue condensation after IAI, associated with a lower IOP increase after injection, suggesting that ONH compliance might buffer the effect of additional intravitreal fluid injection on IOP values.

PMID: 27784074

**Ophthalmologica. 2016 Oct 27. [Epub ahead of print]**

**Characteristics and Predictors of Early and Delayed Responders to Ranibizumab Treatment in Neovascular Age-Related Macular Degeneration: A Retrospective Analysis from the ANCHOR, MARINA, HARBOR, and CATT Trials.**

Gale R, Korobelnik JF, Yang Y, Wong TY.

**PURPOSE:** This retrospective review examined visual acuity (VA) in subjects with neovascular age-related macular degeneration and identified early and delayed response to ranibizumab.

**PROCEDURES:** MARINA, ANCHOR, HARBOR, and CATT published data were examined for response with monthly versus individualized dosing and predictors of early versus delayed response.

**RESULTS:** Data were available for 1,631 subjects; 18-29% were early gainers and 15-16% were delayed gainers. Of the early gainers, 72-83% maintained their best-corrected VA gain at month 12 with monthly or individualized dosing. Delayed gainers in HARBOR almost reached the same level of response as early gainers by 12 months who were able to maintain their response. The main predictor of response was baseline VA.

**CONCLUSION:** There are two distinct types of ranibizumab response; some responded by month 3, while others took up to 12 months. In delayed responders, this may have implications for switching or not switching therapies.

PMID: 27784021

**Handb Exp Pharmacol. 2016 Oct 26. [Epub ahead of print]**

**Anti-angiogenic Therapy for Retinal Disease.**

Paulus YM, Sodhi A.

**Abstract:** Recent breakthroughs in our understanding of the molecular pathophysiology of retinal vascular disease have allowed us to specifically target pathological angiogenesis while minimizing damage to the neurosensory retina. This is perhaps best exemplified by the development of therapies targeting the potent angiogenic growth factor and vascular permeability mediator, vascular endothelial growth factor (VEGF). Anti-VEGF therapies, initially introduced for the treatment of choroidal neovascularization in patients with age-related macular degeneration, have also had a dramatic impact on the management of retinal vascular disease and are currently an indispensable component for the treatment of macular edema in patients with diabetic eye disease and retinal vein occlusions. Emerging evidence supports expanding the use of therapies targeting VEGF for the treatment of retinal neovascularization in patients with diabetic retinopathy and retinopathy of prematurity. However, VEGF is among a growing list of angiogenic and vascular hyperpermeability factors that promote retinal vascular disease. Many of these mediators are expressed in response to stabilization of a single family of transcription factors, the hypoxia-inducible factors (HIFs), that regulate the expression of these angiogenic stimulators. Here we review the basic principles driving pathological angiogenesis and discuss the current state of retinal anti-angiogenic pharmacotherapy as well as future directions.

PMID: 27783271

**Acta Ophthalmol. 2016 Oct 25. [Epub ahead of print]**

**A minimally invasive adjustable-depth blunt injector for delivery of pharmaceuticals into the posterior pole.**

Rotenstreich Y, Tzameret A, Kalish SE, Bubis E, Belkin M, Moroz I, Rosner M, Levy I, Margel S, Sher I.

**PURPOSE:** To investigate the feasibility and safety of a novel minimally invasive adjustable-depth blunt injector for pharmaceuticals delivery into the posterior segment.

**METHODS:** Indocyanine green (ICG), sodium fluorescein and iron oxide nanoparticles (IONPs) were injected using the new injector into the extravascular spaces of the choroid (EVSC) compartment of rabbits and cadaver pig eyes. Spectral domain optical coherence tomography (SD-OCT), fundus imaging and histology analysis were performed for assessment of injection safety and efficacy.

**RESULTS:** Indocyanine green, fluorescein and IONPs were detected across the EVSC in rabbit eyes, covering over 80 per cent of the posterior eye surface. Injected IONPs were retained in the EVSC for at least 2 weeks following injection. No retinal detachment, choroidal haemorrhage or inflammation was detected in any of the injected eyes. In cadaver pig eyes, ICG was detected across the EVSC.

**CONCLUSIONS:** This novel minimally invasive delivery system may be used to safely deliver large volumes of pharmaceuticals into a new treatment reservoir compartment - the EVSC which can serve as a depot, in close proximity to the retina, covering most of the surface of the back of the eye without insertion of surgical instruments under the central retina. This system is predicted to enhance the therapeutic effect of treatments for posterior eye disorders.

PMID: 27778476

**Eur J Ophthalmol. 2016 Feb 3:0. [Epub ahead of print]**

**Comparison of choroidal thickness changes following intravitreal dexamethasone, ranibizumab, and triamcinolone in eyes with retinal vein occlusion.**

Yumusak E, Ornek K, Dikel NH.

**PURPOSE:** To evaluate short-term choroidal thickness changes following intravitreal dexamethasone implant (DEX), ranibizumab (RAN), and triamcinolone acetonide (TA) in eyes with retinal vein occlusion (RVO) and macular edema (ME).

**METHODS:** In this prospective study, 35 eyes of 35 patients with RVO and ME who were treated with intravitreal injections of DEX, RAN, and TA were included. Choroidal thickness was measured using semiautomated segmentation of enhanced depth imaging with optical coherence tomography at fovea and parafoveal areas. Changes in choroidal thickness following treatment were compared statistically.

**RESULTS:** Choroidal thickness decreased following DEX, RAN, and TA treatments (all  $p < 0.05$ ). In the DEX group, at the first month nasal 1,500  $\mu\text{m}$  (N11,500) and at the third month subfoveal (SF3) and nasal 500  $\mu\text{m}$  (N3500) choroidal thickness revealed a significant reduction compared to RAN and TA groups (all  $p < 0.05$ ). In the TA group, choroidal thickness showed a significant reduction only at nasal 1,500  $\mu\text{m}$  (N31,500) at the third month ( $p < 0.05$ ).

**CONCLUSIONS:** Choroidal thickness was decreased in all 3 groups. The DEX and TA groups showed a significant reduction at some areas. Ranibizumab had the smallest effect on choroidal thickness after 3 months among all groups.

PMID: 26847213

## Other treatment & diagnosis

**Ophthalmology. 2016 Oct 25. [Epub ahead of print]**

**Optical Coherence Tomography Reflective Drusen Substructures Predict Progression to Geographic Atrophy in Age-related Macular Degeneration.**

Veerappan M, El-Hage-Sleiman AM, Tai V, Chiu SJ, Winter KP, Stinnett SS, Hwang TS, Hubbard GB 3rd, Michelson M, Gunther R, Wong WT, Chew EY, Toth CA; Age-related Eye Disease Study 2 Ancillary Spectral Domain Optical Coherence Tomography Study Group.

**PURPOSE:** Structural and compositional heterogeneity within drusen comprising lipids, carbohydrates, and proteins have been previously described. We sought to detect and define phenotypic patterns of drusen heterogeneity in the form of optical coherence tomography-reflective drusen substructures (ODS) and examine their associations with age-related macular degeneration (AMD)-related features and AMD progression.

**DESIGN:** Retrospective analysis in a prospective study.

**PARTICIPANTS:** Patients with intermediate AMD (n = 349) enrolled in the multicenter Age-Related Eye Disease Study 2 (AREDS2) ancillary spectral-domain optical coherence tomography (SD OCT) study.

**METHODS:** Baseline SD OCT scans of 1 eye per patient were analyzed for the presence of ODS. Cross-sectional and longitudinal associations of ODS presence with AMD-related features visible on SD OCT and color photographs, including drusen volume, geographic atrophy (GA), and preatrophic features, were evaluated for the entire macular region. Similar associations were also made locally within a 0.5-mm-diameter region around individual ODS and corresponding control region without ODS in the same eye.

**MAIN OUTCOME MEASURES:** Preatrophy SD OCT changes and GA, central GA, and choroidal neovascularization (CNV) from color photographs.

**RESULTS:** Four phenotypic subtypes of ODS were defined: low reflective cores, high reflective cores, conical debris, and split drusen. Among the 349 participants, there were 307 eligible eyes and 74 (24%) had at least 1 ODS. The ODS at baseline were associated with (1) greater macular drusen volume at baseline ( $P < 0.001$ ), (2) development of preatrophic changes at year 2 ( $P = 0.001-0.01$ ), and (3) development of macular GA ( $P = 0.005$ ) and preatrophic changes at year 3 ( $P = 0.002-0.008$ ), but not development of CNV. The ODS at baseline in a local region were associated with (1) presence of preatrophic changes at baseline ( $P = 0.02-0.03$ ) and (2) development of preatrophic changes at years 2 and 3 within the region ( $P = 0.008-0.05$ ).

**CONCLUSIONS:** Optical coherence tomography-reflective drusen substructures are optical coherence tomography-based biomarkers of progression to GA, but not to CNV, in eyes with intermediate AMD. Optical coherence tomography-reflective drusen substructures may be a clinical entity helpful in monitoring AMD progression and informing mechanisms in GA pathogenesis.

PMID: 27793356

**Ophthalmic Physiol Opt. 2016 Nov;36(6):632-642.**

**Collaborative care of non-urgent macular disease: a study of inter-optometric referrals.**

Ly A, Nivison-Smith L, Hennessy MP, Kalloniatis M.

**PURPOSE:** Diseases involving the macula and posterior pole are leading causes of visual impairment and blindness worldwide and may require prompt ophthalmological care. However, access to eye-care and timely patient management may be limited due to inefficient and inappropriate referrals between primary eye-care providers and ophthalmology. Optometrists with a special interest in macular disease may be useful as a community aid to better stratify and recommend best-practice management plans for suitable patients. This study assesses such a notion by appraising the optometric referral patterns of patients with suspected macular disease to an intermediate-tier optometric imaging clinic.

**METHODS:** We performed a retrospective review of patient records and referrals using patients examined at Centre for Eye Health (CFEH) for an initial or follow up macular assessment between the 1/7/2013 and 30/6/2014 (n = 291). The following data were analysed: patient demographic characteristics, primary reason for referral, diagnosed/suspected condition, CFEH diagnosis and recommended management plan.

Macular Disease Foundation Australia Suite 902, 447 Kent Street, Sydney, NSW, 2000, Australia.

Tel: +61 2 9261 8900 | Fax: +61 2 9261 8912 | E: [research@mdfoundation.com.au](mailto:research@mdfoundation.com.au) | W: [www.mdfoundation.com.au](http://www.mdfoundation.com.au)

**RESULTS:** The number of referrals stipulating a diagnosis, confirmed after evaluation at CFEH was 121 of 291 (42%). After evaluation at CFEH, the number of cases without a specific diagnosis was approximately halved (reduced from 47% to 23%), while the number of cases with no apparent defect or normal aging changes rose from 1% to 15%. Overall diagnostic congruency for specified macular conditions was high (58-94%); cases were seldom (30/291, 10%) found to have a completely different macular condition. 244 of 291 (84%) patients seen at CFEH were recommended ongoing optometric care: either with the referring optometrist or through recall to CFEH. Referral to an ophthalmologist was recommended in 47 instances (16%).

**CONCLUSIONS:** More widespread adoption of intermediate-tier optometric eye-care referral pathways in macular disease (following opportunistic primary care screening) has the potential to reduce the number of cases with non-specific diagnoses and to increase those with a diagnosis of normal aging changes or no apparent disease. The majority of cases seen under this intermediate-tier model required ongoing optometric care only and did not require face-to-face consultation with an ophthalmologist.

PMID: 27790767

#### **Data Brief. 2016 Aug 4;9:673-675. eCollection 2016.**

##### **Central visual field sensitivity data from microperimetry with spatially dense sampling.**

Astle AT, Ali I, Denniss J.

**Abstract:** Microperimetry, also referred to as fundus perimetry or fundus-driven perimetry, enables simultaneous acquisition of visual sensitivity and eye movement data. We present sensitivity data collected from 60 participants with normal vision using gaze-contingent perimetry. A custom designed spatially dense test grid was used to collect data across the visual field within 13° of fixation. These data are supplemental to a study in which we demonstrated a spatial interpolation method that facilitates comparison of acquired data from any set of spatial locations to normative data and thus screening of individuals with both normal and non-foveal fixation (Denniss and Astle, 2016) [1].

PMID: 27790630

#### **Retina. 2016 Oct 26. [Epub ahead of print]**

##### **CLINICAL TRIAL ENDPOINTS FOR OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.**

Cole ED, Ferrara D, Novais EA, Louzada RN, Waheed NK.

**PURPOSE:** To describe qualitative and quantitative optical coherence tomography (OCT) angiography (OCTA) parameters for choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) and their applicability as potential clinical trial endpoints.

**METHODS:** A review of current literature related to the topic of OCTA and AMD.

**RESULTS:** There are a number of promising OCTA parameters that can be used to diagnose the presence of CNV and to monitor the activity and progression of the lesion, pre- and post-treatment morphological characteristics, CNV dimensions, and automated quantitative parameters such as vessel density.

**CONCLUSION:** The OCTA parameters described in this review have promise for the future development of clinical trial endpoints, but require further validation before they can be widely used.

PMID: 27787449

**Retin Cases Brief Rep. 2016 Sep 30. [Epub ahead of print]**

**DOME-SHAPED MACULOPATHY: ENHANCED VISUALIZATION WITH RADIAL OPTICAL COHERENCE TOMOGRAPHY SCANS.**

Christenbury JG, Phasukkijwatana N, Tan A, Freund KB, Sarraf D.

**PURPOSE:** To describe two cases of dome-shaped macula (DSM) and serous macular detachment, the diagnosis of which was enhanced with a radial optical coherence tomography (OCT) scanning protocol.

**METHODS:** Retrospective case series of DSM associated with serous macular detachment. Multimodal retinal imaging was performed including spectral domain OCT with a radial scan protocol and en face OCT angiography. Anatomical outcomes before and after therapy are presented.

**RESULTS:** Two cases of DSM associated with serous macular detachment are described. The dome-shaped macular bulge was more clearly elicited as the cause of serous macular detachment with the employment of a radial OCT scanning protocol. Subretinal fluid resolved in both cases using either intravitreal aflibercept injection or half-fluence photodynamic therapy. En face OCT angiography of the choroid demonstrated reduction in the caliber of choroidal vessels after treatment.

**CONCLUSION:** A radial OCT scanning protocol should be considered in eyes with suspicion of DSM, especially in myopic eyes with subretinal fluid. Intravitreal aflibercept therapy or photodynamic therapy may be considered as a treatment for serous macular detachment because of DSM.

PMID: 27780183

**Retina. 2016 Nov;36(11):2191-2196.**

**PATTERNS OF FUNDUS AUTOFLUORESCENCE DEFECTS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION SUBTYPES.**

Ozkok A, Sigford DK, Tezel TH.

**PURPOSE:** To test define characteristic fundus autofluorescence patterns of different exudative age-related macular degeneration subtypes.

**METHODS:** Cross-sectional study. Fifty-two patients with choroidal neovascularization because of three different neovascular age-related macular degeneration subtypes were included in the study. Macular and peripheral fundus autofluorescence patterns of study subjects were compared in a masked fashion.

**RESULTS:** Fundus autofluorescence patterns of all three neovascular age-related macular degeneration subtypes revealed similar patterns. However, peripapillary hypo-autofluorescence was more common among patients with polypoidal choroidal vasculopathy (88.2%) compared with patients with retinal angiomatous proliferation (12.5%) and patients without retinal angiomatous proliferation and polypoidal choroidal vasculopathy (21.1%) ( $P < 0.0001$ ).

**CONCLUSION:** Presence of peripapillary fundus autofluorescence defects in neovascular age-related macular degeneration maybe suggestive of polypoidal choroidal vasculopathy as a variant of neovascular age-related macular degeneration.

PMID: 27078800

**Retina. 2016 Jul 12. [Epub ahead of print]**

**CLINICAL SPECTRUM OF MACULAR-FOVEAL CAPILLARIES EVALUATED WITH OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY.**

Cicinelli MV, Carnevali A, Rabiolo A, Querques L, Zucchiatti I, Scorgia V, Bandello F, Querques G.

**PURPOSE:** To describe macular-foveal capillaries (MFC) by means of optical coherence tomography angiography and to identify the clinical spectrum of this angiographic feature.

**METHODS:** Patients with MFC presenting at the Medical Retina & Imaging Unit of the Department of Ophthalmology, University Vita-Salute San Raffaele in Milan were recruited. Patients underwent a complete ophthalmologic examination that included slit-lamp examination, fundus examination, measurement of best-corrected visual acuity, fundus autofluorescence, and spectral-domain optical coherence tomography (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). Fluorescein angiography was performed in selected cases. Optical coherence tomography angiography was performed through Zeiss prototype (AngioPlex, CIRRUS HD-OCT models 5000; Carl Zeiss Meditec, Inc, Dublin, OH).

**RESULTS:** Twelve eyes of 10 consecutive white patients (5 men and 5 women; 50%) presenting MFC were included. Mean age was  $66.2 \pm 10.2$  years (range, 53-79 years); mean best-corrected visual acuity was  $0.1 \pm 0.13$  logarithm of the minimum angle of resolution (range, 0-0.4 logarithm of the minimum angle of resolution, corresponding to 20/20 to 20/50). Mean central macular thickness was  $348 \pm 57.6$   $\mu$ m. Two patients were affected by macular pucker, two by postsurgical macular edema, two by age-related macular degeneration, one by diabetic retinopathy, one by dome-shaped macula, one presented with chronic serous chorioretinopathy, and one with branch artery occlusion. Six eyes disclosed a complete absence of the foveal avascular zone, whereas the six other cases showed a partial foveal avascularity. No significant difference was found between complete and incomplete MFC with regards to best-corrected visual acuity ( $P = 0.272$ ) and central macular thickness ( $P = 0.870$ ).

**CONCLUSION:** Cases of persistent MFC are heterogeneous in demographic characteristics, fundus appearance, and visual function. However, MFC, presenting either as complete absence of the foveal avascular zone or only partial foveal avascularity, may complicate different retinal abnormalities or represents a coincident finding.

PMID: 27780174

**Retina. 2016 Nov;36(11):2175-2182.**

# **PROGNOSTIC VALUE OF HYPERREFLECTIVE FOCI IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH BEVACIZUMAB.**

Segal O, Barayev E, Nemet AY, Geffen N, Vainer I, Mimouni M.

**PURPOSE:** To study the prognostic value of optical coherence tomography hyperreflective foci (HF) in neovascular age-related macular degeneration.

**METHODS:** Charts of naive neovascular age-related macular degeneration eyes treated with intravitreal bevacizumab between January 2011 and January 2014 were reviewed, and optical coherence tomography was collected at baseline, 3 months, and 12 months. The presence, location (inner vs. outer retinal layers), and number (few = [0-10], moderate [11-20], many [ $>20$ ]) of HF were graded.

**RESULTS:** Overall, charts of 111 eyes were reviewed and 76 eyes of 73 patients fulfilled inclusion criteria. Baseline best-corrected visual acuity was lower in eyes with HF  $> 20$  ( $P = 0.001$ ), inner layer HF ( $P = 0.009$ ), increased central retinal thickness ( $P < 0.001$ ), and intraretinal fluid ( $P < 0.001$ ). Baseline HF  $> 20$  ( $P = 0.002$ ), inner layer HF ( $P = 0.01$ ), increased central retinal thickness ( $P < 0.001$ ), and intraretinal fluid ( $P = 0.001$ ) had worst best-corrected visual acuity at 12 months. Eyes with intraretinal fluid, HF  $> 20$ , and HF adjacent to intraretinal fluid demonstrated a greater reduction in central retinal thickness; only baseline HF  $> 20$  remained significant in multivariate analysis ( $P < 0.001$ ). Eyes with a reduction in HF ( $P = 0.02$ ) and resolution of inner layer HF ( $P = 0.01$ ) had a greater central retinal thickness reduction.

**CONCLUSION:** Quantity and location of HF are of prognostic value in intravitreal bevacizumab-treated naive neovascular age-related macular degeneration. Increased awareness of specialists interpreting

optical coherence tomography scans toward the number and location of HF is prudent.

PMID: 27078799

## Pathogenesis

**Nutrients. 2016 Oct 22;8(10).**

### **The Association between the Lipids Levels in Blood and Risk of Age-Related Macular Degeneration.**

Wang Y, Wang M, Zhang X, Zhang Q, Nie J, Zhang M, Liu X, Ma L.

**Abstract:** Lipid metabolism may be involved in the pathogenic mechanism of age-related macular degeneration (AMD). However, conflicting results have been reported in the associations of AMD with blood lipids. We performed a meta-analysis including a total of 19 studies to evaluate associations between blood lipids and this disease. The result reported that the high level of high-density lipoprotein cholesterol (HDL-C) obtained with an increment of 1 mmol/L could result in a significantly increase in the AMD risk of approximately 18% (relative risk (RR), 1.18; 95% confidence interval (CI), 1.01 to 1.35;  $I^2 = 53.8\%$ ;  $p = 0.007$ ). High levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were significantly associated with a decreased risk of AMD (RRs ranging from 0.92 to 0.95; all  $p < 0.05$ ). The stratified analysis based on AMD subtypes showed that these blood lipids were only significantly associated with the risk of early AMD (all  $p < 0.05$ ). The association between the blood lipids and AMD risk did not differ substantially based on the other characteristics of the participants. A high HDL-C level was associated with an increased AMD risk, whereas participants with high TC, LDL-C, and TG concentrations may show a decreased risk for this disease. Further well-designed large studies are warranted to confirm the conclusions.

PMID: 27782072

**Front Mol Biosci. 2016 Oct 13;3:67. eCollection 2016.**

### **Designer Leptin Receptor Antagonist Allo-aca Inhibits VEGF Effects in Ophthalmic Neoangiogenesis Models.**

Coroniti R, Fario R, Nuno DJ, Otvos L, Scolaro L, Surmacz E.

**Abstract:** Experimental and clinical data suggest that pro-angiogenic, pro-inflammatory and mitogenic cytokine leptin can be implicated in ocular neovascularization and other eye pathologies. At least in part, leptin action appears to be mediated through functional interplay with vascular endothelial growth factor (VEGF). VEGF is a potent regulator of neoangiogenesis and vascular leakage with a proven role in conditions such as proliferative diabetic retinopathy, age-related macular degeneration and diabetic macular edema. Accordingly, drugs targeting VEGF are becoming mainstream treatments for these diseases. The crosstalk between leptin and VEGF has been noted in different tissues, but its involvement in the development of eye pathologies is unclear. Leptin is coexpressed with VEGF during ocular neovascularization and can potentiate VEGF synthesis and angiogenic function. However, whether or not VEGF regulates leptin expression or signaling has never been studied. Consequently, we addressed this aspect of leptin/VEGF crosstalk in ocular models, focusing on therapeutic exploration of underlying mechanisms. Here we show, for the first time, that in retinal (RF/6A) and corneal (BCE) endothelial cells, VEGF (100 ng/mL, 24 h) stimulated leptin mRNA synthesis by 70 and 30%, respectively, and protein expression by 56 and 28%, respectively. In parallel, VEGF induced RF/6A and BCE cell growth by 33 and 20%, respectively. In addition, VEGF upregulated chemotaxis and chemokinesis in retinal cells by ~40%. VEGF-dependent proliferation and migration were significantly reduced in the presence of the leptin receptor antagonist, Allo-aca, at 100-250 nmol/L concentrations. Furthermore, Allo-aca suppressed VEGF-dependent long-term (24 h), but not acute (15 min) stimulation of the Akt and ERK1/2 signaling pathways. The efficacy of Allo-aca was validated in the rat laser-induced choroidal neovascularization model where

the compound (5 µg/eye) significantly reduced pathological vascularization with the efficacy similar to that of a standard treatment (anti-VEGF antibody, 1 µg/eye). Cumulatively, our results suggest that chronic exposure to VEGF upregulates leptin expression and function. As leptin can in turn activate VEGF, the increased abundance of both cytokines could amplify pro-angiogenic and pro-inflammatory environment in the eye. Thus, combined therapies targeting ObR and VEGF should be considered in the treatment of ocular diseases.

PMID: 27790618

**PLoS One. 2016 Oct 27;11(10):e0165653. eCollection 2016.**

**P2Y1 Receptor Signaling Contributes to High Salt-Induced Priming of the NLRP3 Inflammasome in Retinal Pigment Epithelial Cells.**

Prager P, Hollborn M, Steffen A, Wiedemann P, Kohen L, Bringmann A.

**BACKGROUND:** Systemic hypertension is a risk factor of age-related macular degeneration (AMD), a chronic inflammatory disease. Acute hypertension is caused by increased extracellular osmolarity after intake of dietary salt (NaCl). We determined in cultured human retinal pigment epithelial (RPE) cells whether high extracellular NaCl alters the gene expression of inflammasome-associated proteins, and whether autocrine/paracrine purinergic (P2) receptor signaling contributes to the NaCl-induced NLRP3 gene expression.

**METHODOLOGY/PRINCIPAL FINDINGS:** Hyperosmolarity was induced by the addition of 100 mM NaCl or sucrose to the culture medium. Gene and protein expression levels were determined with real-time RT-PCR and Western blot analysis, respectively. IL-1β and IL-18 levels were evaluated with ELISA. Nuclear factor of activated T cell 5 (NFAT5) expression was knocked down with siRNA. High extracellular NaCl induced NLRP3 and pro-IL-1β gene expression, while the gene expression of further inflammasome-associated proteins (NLRP1, NLRP2, NLRP6, NLRP7, NLRP12, NLRC4, AIM2, ASC, procaspase-1, pro-IL-18) was not altered or below the detection threshold. The NaCl-induced NLRP3 gene expression was partially dependent on the activities of phospholipase C, IP3 receptors, protein kinase C, the serum and glucocorticoid-regulated kinase, p38 MAPK, ERK1/2, JNK, PI3K, and the transcription factors HIF-1 and NFAT5. Pannexin-dependent ATP release and P2Y1 receptor activation is required for the full induction of NLRP3 gene expression. High NaCl induced a transient increase of the NLRP3 protein level and a moderate NLRP3 inflammasome activation, as indicated by the transient increase of the cytosolic level of mature IL-1β. High NaCl also induced secretion of IL-18.

**CONCLUSION:** High extracellular NaCl induces priming of the NLRP3 inflammasome in RPE cells, in part via P2Y1 receptor signaling. The inflammasome priming effect of NaCl suggests that high intake of dietary salt may promote local retinal inflammation implicated in the development of AMD.

PMID: 27788256

**Apoptosis. 2016 Oct 24. [Epub ahead of print]**

**Insights on the involvement of (-)-epigallocatechin gallate in ER stress-mediated apoptosis in age-related macular degeneration.**

Karthikeyan B, Harini L, Krishnakumar V, Kannan VR, Sundar K, Kathiresan T.

**Abstract:** Endoplasmic reticulum (ER) stress-mediated apoptosis is a well-known factor in the pathogenesis of age-related macular degeneration (AMD). ER stress leads to accumulation of misfolded proteins, which in turn activates unfolded protein response (UPR) of the cell for its survival. The prolonged UPR of ER stress promotes cell death; however, the transition between adaptation and ER stress-induced apoptosis has not been clearly understood. Hence, the present study investigates the regulatory effect of (-)-epigallocatechin gallate (EGCG) on ER stress-induced by hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and disturbance of

calcium homeostasis by thapsigargin (TG) in mouse retinal pigment epithelial (MRPE) cells. The oxidant molecules influenced MRPE cells showed an increased level of intracellular calcium  $[Ca^{2+}]_i$  in ER and transferred to mitochondria through ER-mitochondrial tether site then increased ROS production. EGCG restores  $[Ca^{2+}]_i$  homeostasis by decreasing ROS production through inhibition of prohibitin1 which regulate ER-mitochondrial tether site and inhibit apoptosis. Effect of EGCG on ER stress-mediated apoptosis was elucidated by exploring the UPR signalling pathways. EGCG downregulated GRP78, CHOP, PERK, ERO1 $\alpha$ , IRE1 $\alpha$ , cleaved PARP, cleaved caspase 3, caspase 12 and upregulated expression of calnexin in MRPE cells. In addition to this, inhibition of apoptosis by EGCG was also confirmed with expression of proteins Akt, PTEN and GSK3 $\beta$ . MRPE cells with EGCG upregulates phosphorylation of Akt at ser473 and phospho ser380 of PTEN, but phosphorylation at ser9 of GSK3 $\beta$  was inhibited. Further, constitutively active (myristoylated) CA-Akt transfected in MRPE cells had an increased Akt activity in EGCG influenced cells. These findings strongly suggest that antioxidant molecules inhibit cell death through the proper balancing of  $[Ca^{2+}]_i$  and ROS production in order to maintain UPR of ER in MRPE cells. Thus, modulation of UPR signalling may provide a potential target for the therapeutic approaches of AMD.

PMID: 27778132

## Epidemiology

**Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5758-5763.**

### **Association of ABCG1 With Neovascular Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy in Chinese and Japanese.**

Ma L, Liu K, Tsujikawa M, Chen H, Brelen ME, Chan VC, Lai TY, Sayanagi K, Hara C, Hashida N, Tam PO, Young AL, Chen W, Nishida K, Pang CP, Chen LJ.

**PURPOSE:** We investigated the association of the ATP-binding cassette, subfamily G, member 1 (ABCG1) gene with polypoidal choroidal vasculopathy (PCV) and neovascular age-related macular degeneration (nAMD) in independent Chinese and Japanese cohorts.

**METHODS:** A total of 12 haplotype-tagging single-nucleotide polymorphisms (SNPs) and the SNP rs57137919 in the ABCG1 gene were first analyzed in a Hong Kong Chinese cohort of 235 nAMD, 236 PCV, and 365 controls, using TaqMan genotyping assays. Two SNPs (rs57137919 and rs225396) that showed a disease-association were genotyped in a Shantou Chinese cohort of 189 nAMD, 187 PCV, and 670 controls, and an Osaka Japanese cohort of 192 nAMD, 204 PCV, and 157 controls, totaling 2435 subjects. Association analysis was performed in individual cohorts, followed by a pooled analysis of the data from all three cohorts.

**RESULTS:** In the Hong Kong cohort, SNP rs57137919 was associated with PCV (odds ratio [OR] = 1.35). A tagging SNP rs225396 was associated with nAMD (OR = 1.28) and PCV (OR = 1.32). In the Osaka cohort, SNP rs225396 was associated with nAMD (OR = 1.42) and PCV (OR = 1.74). In the pooled analysis involving the 3 study cohorts, rs225396 showed an enhanced association with nAMD ( $P = 0.01$ , OR = 1.21,  $I^2 = 14\%$ ) and PCV ( $P = 0.0001$ , OR = 1.35,  $I^2 = 46\%$ ).

**CONCLUSIONS:** In this study, we have newly identified a haplotype-tagging SNP, rs225396, in ABCG1 to be associated with PCV and nAMD in Chinese and Japanese cohorts. This provides new evidence to support ABCG1 as a susceptibility gene for PCV and nAMD. Further replication in other populations should be warranted.

PMID: 27787563

## Genetics

Int Ophthalmol. 2016 Oct 24. [Epub ahead of print]

### **C-reactive protein and complement factor H polymorphism interaction in advanced exudative age-related macular degeneration.**

Soheilian R, Jabbarpour Bonyadi MH, Moein H, Babanejad M, Ramezani A, Yaseri M, Soheilian M.

**PURPOSE:** To determine the association of C-reactive protein (CRP) and complement factor H (CFH) gene with exudative age-related macular degeneration (AMD) and any possible interaction among these factors.

**METHODS:** In this case-control study, 139 unrelated patients with exudative AMD and 123 non-AMD controls were recruited. Blood sample was taken for analysis of the CRP levels and DNA testing. DNA fragments of CFH gene variants containing 4 single nucleotide polymorphisms including rs800292, rs1061170, rs2274700, and rs3753395 were assessed. A CRP level of  $\geq 3$  mg/L was considered as elevated. The association of elevated CRP and CFH gene variants polymorphism with exudative AMD was compared between the groups.

**RESULTS:** Mean age was  $72.6 \pm 6.4$  for controls and  $74.9 \pm 7.4$  for case group ( $P = 0.006$ ). The difference between CRP levels in cases and controls was not statistically significant ( $P = 0.055$ ). However, Y402H variant of CFH in both homozygous and heterozygous carriers C allele was significantly more frequent among exudative AMD patients than controls, 32.1 versus 6.5 % ( $P < 0.001$ ). Evaluating various CRP levels in patients with CC and non-CC genotypes disclosed that in CC genotype group, higher CRP level ( $>3$  mg/L) was associated with higher risk of developing exudative AMD (OR = 12.0, CI: 1.5-98.8) compared with the control group.

**CONCLUSION:** This study disclosed no difference in CRP levels per se between exudative AMD patients with control group. However, higher levels of CRP in the presence of C allele of Y402H might confer more risk for the development of exudative AMD.

PMID: 27778189

Mol Vis. 2016 Oct 17;22:1239-1247. eCollection 2016.

### **North Carolina macular dystrophy (MCDR1) caused by a novel tandem duplication of the PRDM13 gene.**

Bowne SJ, Sullivan LS, Wheaton DK, Locke KG, Jones KD, Koboldt DC, Fulton RS, Wilson RK, Blanton SH, Birch DG, Daiger SP.

**PURPOSE:** To identify the underlying cause of disease in a large family with North Carolina macular dystrophy (NCMD).

**METHODS:** A large four-generation family (RFS355) with an autosomal dominant form of NCMD was ascertained. Family members underwent comprehensive visual function evaluations. Blood or saliva from six affected family members and three unaffected spouses was collected and DNA tested for linkage to the MCDR1 locus on chromosome 6q12. Three affected family members and two unaffected spouses underwent whole exome sequencing (WES) and subsequently, custom capture of the linkage region followed by next-generation sequencing (NGS). Standard PCR and dideoxy sequencing were used to further characterize the mutation.

**RESULTS:** Of the 12 eyes examined in six affected individuals, all but two had Gass grade 3 macular degeneration features. Large central excavation of the retinal and choroid layers, referred to as a macular caldera, was seen in an age-independent manner in the grade 3 eyes. The calderas are unique to affected individuals with MCDR1. Genome-wide linkage mapping and haplotype analysis of markers from the chromosome 6q region were consistent with linkage to the MCDR1 locus. Whole exome sequencing and custom-capture NGS failed to reveal any rare coding variants segregating with the phenotype. Analysis of

the custom-capture NGS sequencing data for copy number variants uncovered a tandem duplication of approximately 60 kb on chromosome 6q. This region contains two genes, CCNC and PRDM13. The duplication creates a partial copy of CCNC and a complete copy of PRDM13. The duplication was found in all affected members of the family and is not present in any unaffected members. The duplication was not seen in 200 ethnically matched normal chromosomes.

**CONCLUSIONS:** The cause of disease in the original family with MCDR1 and several others has been recently reported to be dysregulation of the PRDM13 gene, caused by either single base substitutions in a DNase 1 hypersensitive site upstream of the CCNC and PRDM13 genes or a tandem duplication of the PRDM13 gene. The duplication found in the RFS355 family is distinct from the previously reported duplication and provides additional support that dysregulation of PRDM13, not CCNC, is the cause of NCMD mapped to the MCDR1 locus.

PMID: 27777503

## Stem cells

**Prog Retin Eye Res. 2016 Oct 23. [Epub ahead of print]**

### **Advances in bone marrow stem cell therapy for retinal dysfunction.**

Park SS, Moisseiev E, Bauer G, Anderson JD, Grant MB, Zam A, Zawadzki RJ, Werner JS, Nolta JA.

**Abstract:** The most common cause of untreatable vision loss is dysfunction of the retina. Conditions, such as age-related macular degeneration, diabetic retinopathy and glaucoma remain leading causes of untreatable blindness worldwide. Various stem cell approaches are being explored for treatment of retinal regeneration. The rationale for using bone marrow stem cells to treat retinal dysfunction is based on preclinical evidence showing that bone marrow stem cells can rescue degenerating and ischemic retina. These stem cells have primarily paracrine trophic effects although some cells can directly incorporate into damaged tissue. Since the paracrine trophic effects can have regenerative effects on multiple cells in the retina, the use of this cell therapy is not limited to a particular retinal condition. Autologous bone marrow-derived stem cells are being explored in early clinical trials as therapy for various retinal conditions. These bone marrow stem cells include mesenchymal stem cells, mononuclear cells and CD34+ cells. Autologous therapy requires no systemic immunosuppression or donor matching. Intravitreal delivery of CD34+ cells and mononuclear cells appears to be tolerated and is being explored since some of these cells can home into the damaged retina after intravitreal administration. The safety of intravitreal delivery of mesenchymal stem cells has not been well established. This review provides an update of the current evidence in support of the use of bone marrow stem cells as treatment for retinal dysfunction. The potential limitations and complications of using certain forms of bone marrow stem cells as therapy are discussed. Future directions of research include methods to optimize the therapeutic potential of these stem cells, non-cellular alternatives using extracellular vesicles, and in vivo high-resolution retinal imaging to detect cellular changes in the retina following cell therapy.

PMID: 27784628

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