**Drug treatment**

*Ophthalmology. 2018 Jan 19. [Epub ahead of print]*

**Efficacy and Safety of Ranibizumab 0.5 mg for the Treatment of Macular Edema Resulting from Uncommon Causes: Twelve-Month Findings from PROMETHEUS.**


**PURPOSE:** To evaluate the efficacy and safety of ranibizumab 0.5 mg in adult patients with macular edema (ME) resulting from any cause other than diabetes, retinal vein occlusion, or neovascular age-related macular degeneration.

**DESIGN:** A phase 3, 12-month, double-masked, randomized, sham-controlled, multicenter study.

**PARTICIPANTS:** One hundred seventy-eight eligible patients aged ≥18 years.

**METHODS:** Patients were randomized 2:1 to receive either ranibizumab 0.5 mg (n = 118) or sham (n = 60) at baseline and month 1. From month 2, patients in both arms received open-label individualized ranibizumab treatment based on disease activity. A preplanned subgroup analysis was conducted on the primary end point on 5 predefined baseline ME etiologies (inflammatory/post-uveitis, pseudophakic or aphakic, central serous chorioretinopathy, idiopathic, and miscellaneous).

**MAIN OUTCOME MEASURES:** Changes in best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study letters) from baseline to month 2 (primary end point) and month 12 and safety over 12 months.

**RESULTS:** Overall, 156 patients (87.6%) completed the study. The baseline characteristics were well balanced between the treatment arms. Overall, ranibizumab showed superior efficacy versus sham from baseline to month 2 (least squares mean BCVA, +5.7 letters vs. +2.9 letters; 1-sided P = 0.0111), that is, a treatment effect (TE) of +2.8 letters. The mean BCVA gain from baseline to month 12 was 9.6 letters with ranibizumab. The TE at month 2 was variable in the 5 predefined etiology subgroups, ranging from >5-letter gain to 0.5-letter loss. The safety findings were consistent with the well-established safety profile of ranibizumab.

**CONCLUSIONS:** The primary end point was met and ranibizumab showed superiority in BCVA gain over sham in treating ME due to uncommon causes, with a TE of +2.8 letters versus sham at month 2. At month 12, the mean BCVA gain was high (9.6 letters) in the ranibizumab arm; however, the TE was observed to be variable across the different etiology subgroups, reaching a >1-line TE in BCVA in patients with ME resulting from inflammatory conditions/post-uveitis or after cataract surgery. Overall, ranibizumab was well tolerated with no new safety findings up to month 12.

PMID: 29371007
MACULAR ATROPHY INCIDENCE IN ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR-TREATED NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: Risk Factor Evaluation for Individualized Treatment Need of Ranibizumab or Aflibercept According to an Observe-and-Plan Regimen.

Mantel I, Dirani A, Zola M, Parvin P, De Massougnes S, Bergin C.

PURPOSE: To investigate factors associated with macular atrophy (MA) incidence in neovascular age-related macular degeneration treated with either ranibizumab or aflibercept in an Observe-and-Plan variable dosing regimen.

METHODS: Information was obtained from two identical prospective treatment protocols using ranibizumab or aflibercept in a variable dosing regimen termed "Observe and Plan." Eyes without MA at baseline were included. New atrophy at the final 2-year visit was investigated with univariate and multivariate analysis to identify associated risk factors, focusing on treatment factors.

RESULTS: De novo MA developed in 63 (42%) of 149 eyes/patients (mean age 79.0 years), in 70 eyes treated using aflibercept and 79 eyes using ranibizumab. The univariate analysis showed multiple associations of MA with baseline factors, of which the following were confirmed as independent risk factors after multivariate stepwise logistic regression: lower number of anti-vascular endothelial growth factors injections (P = 0.011), depigmentation (P = 0.0004), reticular pseudodrusen (P = 0.0005), lower baseline visual acuity (P = 0.0006), and retinal angiomatous proliferation (P = 0.001). The drug type showed no significant association with MA incidence (P = 0.21).

CONCLUSION: Within the variable dosing regimen, MA incidence was higher when fewer injections were required. More injections, if required by disease activity, did not increase the risk for MA. 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: 29370035


Oral Doxycycline Reduces the Total Number of Intraocular Bevacizumab Injections Needed to Control Neovascular Age-related Macular Degeneration.


Abstract: Tetracyclines, especially doxycycline, play a role in the regulation of inflammation, immunomodulation, cell proliferation, and angiogenesis. Treatment of corneal angiogenesis or choroidal neovascularization with tetracyclines has been shown to be effective in animal models. The aim of this study was to evaluate the efficacy of oral doxycycline in reducing the total number of intraocular injections needed for controlling neovascular age-related macular degeneration in human patients. In this interventional case series, 28 random consecutive patients with neovascular age-related macular degeneration from Farabi Eye Hospital, Tehran, Iran were treated for 4 months with 200 mg doxycycline once a day after the first intravitreal bevacizumab injection in addition to standard therapy in agreement with as-needed regimen. After 12 months of follow-up, total number of injections, foveal thickness and visual acuity were compared to those at baseline and of similar studies. Similar to standard treatment, co-treatment with doxycycline was able to control active disease (intraretinal or subretinal fluid or leakage, new-onset of macular hemorrhage, and reduction of visual acuity more than 5 letters based on Early Treatment Diabetic Retinopathy Study [ETDRS] charts) yet with fewer injections (for current study and standard
treatment, respectively 3.14 vs. 5.92, P < 0.001). Furthermore, while better control of the foveal thickness was achieved (P < 0.001), vision improvement was similar to that achieved with standard therapy (P > 0.05). If confirmed in larger studies, the findings of this interventional case series could provide a strategy to control neovascular age-related macular degeneration with fewer intraocular bevacizumab injections by co-administering a well-known oral agent-doxycycline.

PMID: 29367931 PMCID: PMC5776498


Intravitreal injection of aflibercept, an anti-VEGF antagonist, down-regulates plasma von Willebrand factor in patients with age-related macular degeneration.


Abstract: We investigated the association between von Willebrand factor (VWF) and exudative age-related macular degeneration (AMD) in 114 Japanese patients. Intravitreal injection of vascular endothelial growth factor (VEGF) inhibitor is the most effective therapy for AMD. Therefore, we analyzed changes of VWF antigen (VWF:Ag) and VWF multimers (VWFMs) after intravitreal injection of aflibercept, an anti-VEGF antagonist. The relationship between polymorphisms in complement factor H (p.Y402H and p.I62V) and AMD was previously reported. In our patients, p.I62V, but not p.Y402H, was significantly associated with an increased risk of AMD. Pre-treatment plasma levels of VWF:Ag in patients with AMD were significantly higher than those in controls. Unusually large VWFMs (UL-VWFMs) were detected in the majority of AMD patients with concurrent vitreous or subretinal hemorrhage. After intravitreal injection of aflibercept, plasma levels of VWF:Ag and VEGF-A were significantly decreased. UL-VWFMs disappeared after aflibercept injection in three cases, but persisted even 1 month after injection in the other five cases. In conclusion, plasma VWF:Ag levels were significantly elevated in patients with AMD, and decreased after intravitreal aflibercept injection. VWF may play an important role in the pathophysiology of AMD, and aflibercept might improve AMD by reducing plasma levels of VWF in addition to VEGF-A.

PMID: 29367644


Detailed analysis of retinal morphology in patients with diabetic macular edema (DME) randomized to ranibizumab or triamcinolone treatment.

Călugăru D, Călugăru M.


Detailed analysis of retinal morphology in patients with diabetic macular edema (DME) randomized to ranibizumab or triamcinolone treatment - reply to the letter to the editor.

Karst S, Mitsch C, Scholda C, Schmidt-Erfurth U.

PMID: 29368041
Other treatment & diagnosis


Comparison of macular parameters after femtosecond laser-assisted and conventional cataract surgery in age-related macular degeneration.


PURPOSE: To evaluate differences in postoperative central macular thickness, central macular volume, corrected distance visual acuity (CDVA), and number of intravitreal anti-vascular endothelial growth factor (VEGF) injections between conventional and femtosecond laser-assisted cataract surgery in wet age-related macular degeneration (AMD).

SETTING: Tertiary referral center, Lucerne, Switzerland.

DESIGN: Retrospective case series.

METHODS: Consecutive patients with AMD and cataract were enrolled between January 2010 and December 2015. Associations between postoperative changes in central macular thickness, central macular volume, CDVA, and number of anti-VEGF injections with type of surgery were assessed statistically.

RESULTS: The study comprised 140 eyes (110 patients). No differences in postoperative central macular thickness (-9.20 μm; 95% confidence interval [CI], -41.68 to 23.28; P = .576), central macular volume (-0.08 mm2; 95% CI, -0.36 to 0.19; P = .593), visual acuity (0.03 logarithm of the minimum angle of resolution; 95% CI, -0.09 to 0.15; P = .647) or postoperative number of anti-VEGF injections (0.30; 95% CI, 0.45 to 1.05; P = .427) were found between the femtosecond laser group and the conventional group over a mean follow-up of 619 days ± 473 (SD). In the 33 eyes that had optical coherence tomography measurement within a postoperative period of 2 weeks, the central macular volume was significantly lower in femtosecond laser-treated eyes (-0.71 mm2; 95% CI, -1.19 to -0.23; P = .005).

CONCLUSIONS: Overall, the postoperative course between wet AMD after femtosecond laser and conventional cataract surgery was equal. During the early follow-up, femtosecond laser-treated eyes had less subclinical macular edema, indicating a possible benefit for patients with macular vulnerability.

PMID: 29361327

Retina. 2018 Jan 23. [Epub ahead of print]

SUBRETINAL ENDOSCOPIC SURGERY TO TREAT LARGE SUBRETINAL HEMORRHAGES SECONDARY TO AGE-RELATED MACULAR DEGENERATION.

Kaga T, Kojima T, Yokoyama S, Sato H, Yoshida N, Ichikawa K.

PURPOSE: To evaluate the potential of subretinal endoscopic surgery as a novel treatment for large subretinal hemorrhage secondary to age-related macular degeneration.

METHODS: Five patients with large subretinal hemorrhage secondary to age-related macular degeneration underwent subretinal endoscopic surgery, with a minimum follow-up of 12 months.

RESULTS: The large subretinal hemorrhage was completely removed by subretinal endoscopic surgery without a large retinotomy in all cases. The fibrovascular pigment epithelial detachment including choroidal neovascularization was completely removed in four cases. In three of these cases, the bleeding was confirmed to be originating from one point of rupture in the Bruch membrane, which was treated by coagulation using intraocular diathermy. Although visual acuity improved in three cases, it deteriorated and remained stable in one case each. Fibrovascular pigment epithelial detachment persisted in one patient...
after surgery; he needed anti-vascular endothelial growth factor therapy, whereas the other four did not because their fibrovascular pigment epithelial detachment was removed. At the final follow-up, no severe postoperative complications, such as retinal detachment or proliferative vitreoretinopathy, were noted.

CONCLUSION: Subretinal endoscopic surgery can completely remove subretinal hemorrhage and fibrovascular pigment epithelial detachment including choroidal neovascularization without a large retinotomy. It also aids in the direct and detailed confirmation of subretinal lesions by ophthalmic endoscope.

PMID: 29370029


Retinal vascular alterations in reticular pseudodrusen with and without outer retinal atrophy assessed by optical coherence tomography angiography.

Cicinelli MV, Rabiolo A, Sacconi R, Lamanna F, Querques L, Bandello F, Querques G.

PURPOSE: To investigate the intraretinal structural and vascular alterations in patients featuring reticular pseudodrusen (RPD), RPD with outer retinal atrophy (ORA), and drusen.

DESIGN: Observational cross-sectional study.

METHODS: Clinical practice study including 68 eyes of 57 patients (22 eyes of 17 patients with RPD; 24 eyes of 21 patients with RPD+ORA; 22 eyes of 19 patients with drusen). Each patient underwent spectral-domain optical coherence tomography (OCT) and OCT angiography (OCT-A). Measurement of retinal layers' thickness was obtained by the automated segmentation protocol of the Spectralis OCT (Heidelberg Eye Explorer V.1.9.10.0). The superficial capillary plexus (SCP) and the deep capillary plexus (DCP) vessel density, as well as the size of the foveal avascular zone were calculated on 3×3 OCT-A. Main outcome was to compare vessel density at the SCP and DCP among the groups and controls.

RESULTS: At the SCP, the vessel density was lower in RPD and RPD+ORA patients with respect to controls (P=0.02 and P=0.003, respectively). At the DCP, meaningful disparity was found between the study groups and the healthy subjects in the vessel density (P<0.001, P=0.04 and P=0.001 for RPD, RDP+ORA and drusen, respectively). The ganglion cell layer (GCL) was thinner in all patients affected either by RPD, RPD+ORA or drusen compared with healthy subjects (P=0.02, P=0.03 and P=0.004, respectively).

CONCLUSION: Significant retinal vascular loss is a common feature of patients with non-exudative age-related macular degeneration, more pronounced in those featuring RPD and RPD+ORA. It is associated with retinal thinning, localised particularly at the GCL, compared with controls.

PMID: 29363531

Ophthalmologica. 2018 Jan 19. [Epub ahead of print]

Optical Coherence Tomography Angiography Offers New Insights into Choriocapillaris Perfusion.

Lauermann JL, Eter N, Alten F.

Abstract: The choriocapillaris (CC) represents a fundamentally important vascular layer that is subject to physiologic changes with increasing age and that is also associated with a wide range of chorioretinal diseases. So far, information on blood flow in this specific layer has remained limited. With the advent of optical coherence tomography angiography (OCTA), new perspectives and possibilities of CC imaging have begun to evolve. This article shall review the opportunities and challenges of applying OCTA technology to
the CC layer and summarize the current clinical efforts in OCTA CC imaging exemplarily in dry age-related macular degeneration and central serous chorioretinopathy.

PMID: 29353272

**Pathogenesis**


C-reactive protein and pentraxin-3 binding of factor H-like protein 1 differs from complement factor H: implications for retinal inflammation.


Abstract: Retinal inflammation plays a key role in the progression of age-related macular degeneration (AMD), a condition that leads to loss of central vision. The deposition of the acute phase pentraxin C-reactive protein (CRP) in the macula activates the complement system, thereby contributing to dysregulated inflammation. The complement protein factor H (FH) can bind CRP and down-regulate an inflammatory response. However, it is not known whether a truncated form of FH, called factor H-like protein 1 (FHL-1), which plays a significant regulatory role in the eye, also interacts with CRP. Here, we compare the binding properties of FHL-1 and FH to both CRP and the related protein pentraxin-3 (PTX3). We find that, unlike FH, FHL-1 can bind pro-inflammatory monomeric CRP (mCRP) as well as the circulating pentameric form. Furthermore, the four-amino acid C-terminal tail of FHL-1 (not present in FH) plays a role in mediating its binding to mCRP. PTX3 was found to be present in the macula of donor eyes and the AMD-associated Y402H polymorphism altered the binding of FHL-1 to PTX3. Our findings reveal that the binding characteristics of FHL-1 differ from those of FH, likely underpinning independent immune regulatory functions in the context of the human retina.

PMID: 29374201 D

**Dis Model Mech. 2017 Dec 28. [Epub ahead of print]**

Superior cervical gangliectomy induces non-exudative age-related macular degeneration in mice.

Dieguez HH, Romeo HE, Fleitas MFG, Aranda ML, Milne G, Rosenstein RE, Dorfman D.

Abstract: Non-exudative age-related macular degeneration, a prevalent cause of blindness, is a progressive and degenerative disease, characterized by alterations in Bruch’s membrane, retinal pigment epithelium, and photoreceptors exclusively localized in the macula. Despite there are experimental murine models, the vast majority take too long to develop retinal alterations, which in general are ubiquitous, many result from non-eye specific genetic manipulations, and most do not always reproduce the hallmarks of human age-related macular degeneration. Choroid vessels receive sympathetic innervation from the superior cervical ganglion, which together with the parasympathetic system, regulate the blood flow. Choroid blood flow changes have been involved in age-related macular degeneration development and progression. At present no experimental models take this factor into account. The aim of this work was to analyze the effect of superior cervical gangliectomy on the choroid, Bruch’s membrane, retinal pigment epithelium, and retina. Adult male C57BL/6J mice were submitted to unilateral superior cervical gangliectomy and a contralateral sham procedure. Although superior cervical gangliectomy induced ubiquitous choroid and choriocapillaris changes, it induced Bruch’s membrane thickening, retinal pigment epithelium melanin content and retinoid isomerohydrolase loss, drusen-like deposit occurrence, and retinal pigment epithelium and photoreceptors atrophy, exclusively localized in the temporal side. Moreover, superior cervical gangliectomy provoked a localized increase in retinal pigment epithelium and photoreceptors apoptosis, and photoreceptors electroretinographic function decline. Therefore, superior cervical gangliectomy recapitulated the main
features of human non-exudative age-related macular degeneration, and could become a new experimental model of dry age-related macular degeneration, and a useful platform for developing new therapies.

PMID: 29361515


Altered proportion of CCR2+ and CX3CR1+ circulating monocytes in neovascular age-related macular degeneration and polypoidal choroidal vasculopathy.

Subhi Y, Krogh Nielsen M, Molbech CR, Sørensen TL.

BACKGROUND: We investigated the expression of chemokine receptors CCR2 and CX3CR1 on circulating monocyte subsets in patients with neovascular age-related macular degeneration and patients with polypoidal choroidal vasculopathy.

METHODS: We recruited patients with neovascular age-related macular degeneration, patients with polypoidal choroidal vasculopathy, and age-matched healthy controls for this prospective case-control study. All participants underwent comprehensive clinical examination and imaging. Freshly sampled venous blood was prepared for flow cytometry, where we determined the proportion of CCR2+ and CX3CR1+ positive cells in monocyte subsets identified using monocyte identification and subgrouping surface markers CD14, CD16, and HLA-DR.

RESULTS: Patients with neovascular AMD had significantly increased proportion of CCR2+ and CX3CR1+ non-classical monocytes. PCV type 1 was associated with significantly increased CCR2+ and CX3CR1+ in all monocyte subsets when compared to PCV type 2.

CONCLUSIONS: Neovascular AMD is associated with increased expression of angiogenesis-associated chemokine receptors in the pro-inflammatory non-classical monocytes. PCV differ from neovascular AMD immunologically and show immunological heterogeneity across angiographic subtypes.

PMID: 29360187

Curr Alzheimer Res. 2018 Jan 18. [Epub ahead of print]

AβPP-induced UPR transcriptomic signature of glial cells to oxidative stress as an adaptive mechanism to preserve cell function and survival.

Chalour N, Maoui A, Rat P, Massicot F, Dutot M, Faussat AM, Devevre E, Limb A, Warnet JM, Treton J, Dinet V, Mascarelli F.

BACKGROUND: Alzheimer's disease (AD) and age-related macular degeneration (AMD) present similarities, particularly with respect to oxidative stress, including production of 4-Hydroxy-2-nonenal (HNE). AMD has been named the AD in the eye. The Müller cells (MC) function as a principal glia of the retina and maintain water/potassium, glutamate homeostasis and redox status. Any MC dysfunction results in retinal neurodegeneration.

OBJECTIVES: We investigated the effects of HNE in human MC.

RESULTS: HNE induced an increase of the reactive oxygen species associated with mitochondrial dysfunction and apoptosis. HNE induced endoplasmic reticulum (ER) stress (upregulation of GRP78/Bip, and the proapoptotic factor, CHOP). HNE also impaired expression of genes controlling potassium homeostasis (KCNJ10), glutamate detoxification (GS), and the visual cycle (RLBP1). MC adaptive response to HNE included upregulation of amyloid-β protein precursor (AβPP). To determine the role of AβPP, we overexpressed AβPP in MC. Overexpression of AβPP induced strong antioxidant and anti-ER
stress (PERK downregulation and GADD34 upregulation) responses accompanied by activation of the prosurvival branch of the unfolded protein response. It was also associated with upregulation of major genes involved in MC-controlled retinal homeostasis (KCNJ10, GS, and RLBP1) and protection against HNE-induced apoptosis. Therefore, AβPP is an ER and oxidative stress responsive molecule, and is able to stimulate the transcription of major genes involved in MC functions impaired by HNE.

CONCLUSION: Our study suggests that targeting oxidative and ER stress might be a potential therapeutic strategy against glia impairment in AMD and AD, in light of the common features between the two pathologies.

PMID: 29357794

**Prog Retin Eye Res. 2018 Jan 17. [Epub ahead of print]**

**Epigenetics, microbiota, and intraocular inflammation: New paradigms of immune regulation in the eye.**

Wen X, Hu X, Miao L, Ge X, Deng Y, Bible PW, Wei L.

Abstract: Sight threatening immune responses that damage the eye characterize intraocular inflammatory diseases. These diseases including uveitis and age-related macular degeneration are worryingly common and quality of life shattering. Genetic studies in past decades significantly advanced our understanding of the etiology of these devastating diseases. Unfortunately, patient genetics alone failed to adequately explain disease origin, susceptibility, and progression. Non-genetic factors such as the epigenetic regulation of ocular diseases and the environmental factors triggering intraocular inflammation offer new insight into intraocular inflammatory disorders. Importantly, mounting evidence is signaling that dysbiosis of human microbiota leads to rapid epigenomic reprogramming of host cells and results in the onset of many diseases. In this review, we discuss how epigenetic mechanisms and microbiota may cooperate to initiate and perpetuate ocular inflammation. Lastly, we propose that the discovery of intraocular microbiota presents a significant shift in thought affecting current approaches to the diagnosis, treatment, and prevention of intraocular inflammatory diseases such as uveitis and age-related macular degeneration. The geographical and genetic background difference in both disease presentation and genetic association of intraocular inflammatory diseases may be due to the variation of intraocular microbiota.

PMID: 29357307

**Epidemiology**

**JAMA Ophthalmol. 2018 Jan 25. [Epub ahead of print]**

**Prevalence and Causes of Unilateral Vision Impairment and Unilateral Blindness in Australia: The National Eye Health Survey.**

Foreman J, Xie J, Keel S, Ang GS, Lee PY, Bourne R, Crowston JG, Taylor HR, Dirani M.

IMPORTANCE: This study determines the prevalence of unilateral vision impairment (VI) and unilateral blindness to assist in policy formulation for eye health care services.

OBJECTIVE: To determine the prevalence and causes of unilateral VI and unilateral blindness in Australia.

DESIGN, SETTING, AND PARTICIPANTS: This cross-sectional population-based survey was conducted from March 2015 to April 2016 at 30 randomly selected sites across all strata of geographic remoteness in Australia. A total of 1738 indigenous Australians 40 years or older and 3098 nonindigenous Australians 50 years or older were included.
MAIN OUTCOMES AND MEASURES: The prevalence and causes of unilateral vision impairment and blindness, defined as presenting visual acuity worse than 6/12 and 6/60, respectively, in the worse eye, and 6/12 or better in the better eye.

RESULTS: Of the 1738 indigenous Australians, mean (SD) age was 55.0 (10.0) years, and 1024 participants (58.9%) were female. Among the 3098 nonindigenous Australians, mean (SD) age was 66.6 (9.7) years, and 1661 participants (53.6%) were female. The weighted prevalence of unilateral VI in indigenous Australians was 12.5% (95% CI, 11.0%-14.2%) and the prevalence of unilateral blindness was 2.4% (95% CI, 1.7%-3.3%), respectively. In nonindigenous Australians, the prevalence of unilateral VI was 14.6% (95% CI, 13.1%-16.3%) and unilateral blindness was found in 1.4% (95% CI, 1.0%-1.8%). The age-adjusted and sex-adjusted prevalence of unilateral vision loss was higher in indigenous Australians than nonindigenous Australians (VI: 18.7% vs 14.5%; P = .02; blindness: 2.9% vs 1.3%; P = .02). Risk factors for unilateral vision loss included older age (odds ratio [OR], 1.60 for each decade of age for indigenous Australians; 95% CI, 1.39-1.86; OR, 1.65 per decade for nonindigenous Australians; 95% CI, 1.38-1.96), very remote residence (OR, 1.65; 95% CI, 1.01-2.74) and self-reported diabetes (OR, 1.52; 95% CI, 1.12-2.07) for indigenous Australians, and having not undergone an eye examination in the past 2 years for nonindigenous Australians (OR, 1.54; 95% CI, 1.04-2.27). Uncorrected refractive error and cataract were leading causes of unilateral VI in both populations (70%-75%). Corneal pathology (16.7%) and cataract (13.9%) were leading causes of unilateral blindness in indigenous Australians, while amblyopia (18.8%), trauma (16.7%), and age-related macular degeneration (10.4%) were major causes of unilateral blindness in nonindigenous Australians.

CONCLUSIONS AND RELEVANCE: Unilateral vision loss is prevalent in indigenous and nonindigenous Australians; however, most cases are avoidable. As those with unilateral vision loss caused by cataract and posterior segment diseases may be at great risk of progressing to bilateral blindness, national blindness prevention programs may benefit from prioritising examination and treatment of those with unilateral vision loss.

PMID: 29372249

Eye Contact Lens. 2018 Jan 22. [Epub ahead of print]

Longitudinal Changes in Disc and Retinal Lesions Among Highly Myopic Adolescents in Singapore Over a 10-Year Period.


OBJECTIVES: To examine the progression pattern of disc and retinal lesions in highly myopic Chinese adolescents over a 10-year period in Singapore.

METHODS: This longitudinal study included Chinese participants who showed high myopia (spherical equivalent [SE] worse than or equal to -5 diopters [D]), no history of refractive surgery, and available fundus photographs at both 2006 (baseline) and 2016 (10-year follow-up) visits. Forty-four adolescents (aged 12-16 years at baseline) who were re-examined later at follow-up were included. Cycloplegic refraction, biometry, and fundus photography were performed at both visits. A trained grader classified myopic macular degeneration (MMD) based on the Meta-pathologic myopia classification and disc lesions from fundus photographs. Choroidal thickness (CT) measurements were performed at 10-year follow-up using swept-source optical coherence tomography. The ocular parameters and lesions were compared between baseline and follow-up.

RESULTS: There was a significant worsening of high myopia at follow-up to -7.5±1.8 D (mean SE±SD) in 2016 versus -6.2±1.3 D in 2006; (P<0.001). The 10-year changes included increased degree of tessellation (26 eyes, 29.5%), development of new tessellated fundus (19 eyes, 21.6%), disc tilt (7 eyes, 8.0%), and expansion of peripapillary atrophy size (33 eyes, 37.5%). Eyes with early-onset tessellation (present at
baseline, 48 eyes) showed significantly thinner CT (P<0.05), compared with eyes with late-onset
tessellation (incident at 10-year follow-up, 19 eyes). No cases of MMD were recorded at baseline or 10-
year follow-up.

CONCLUSIONS: Although there was no incident MMD, the retinal and disc lesions worsened over the
follow-up period. Early-onset fundus tessellation was associated with thinner CT.

PMID: 29369230

Ophthalmology. 2018 Jan 20. [Epub ahead of print]

Characterizing Disease Burden and Progression of Geographic Atrophy Secondary to Age-Related
Macular Degeneration.

Chakravarthy U, Bailey CC, Johnston RL, McKibbin M, Khan RS, Mahmood S, Downey L, Dhingra N,
Brand C, Brittain CJ, Willis JR, Rabhi S, Muthutantri A, Cantrell RA.

PURPOSE: To understand levels of disease burden and progression in a real-world setting among patients
from the United Kingdom with bilateral geographic atrophy (GA) secondary to age-related macular
degeneration (AMD).

DESIGN: Retrospective cohort analysis of a multicenter electronic medical record (EMR) database.

PARTICIPANTS: Patients who were aged ≥50 years with bilateral GA and no history of choroidal
neovascularization (CNV) and who attended 1 of 10 clinical sites using the EMR.

METHODS: A deidentified data set was constructed from the records held at the 10 sites. An algorithm was
used to extract cases with a GA diagnosis, of which 1901 had bilateral GA and form the basis of this report.
A sample of records randomly selected from each center was used to validate disease definitions.

MAIN OUTCOME MEASURES: Progression to blindness (visual acuity [VA] <20 letters or Snellen 3/60 in
the better-seeing eye), driving ineligibility (VA ≤70 letters or Snellen 6/12 in the better-seeing eye),
progression to CNV, loss of 10 or more letters, and mean change in VA over time.

RESULTS: At first record of GA, 7.1% had a VA in the better-seeing eye equal to or lower than the cutoff
for blindness registration and 71.1% had a VA that would have rendered them ineligible to drive. Over time,
16% became legally blind (median time to outcome, 6.2 years) and 66.7% became ineligible to drive
(median time to outcome, 1.6 years). In the worse-seeing eye, 40.1% lost ≥10 letters in 2.4 years. Among
patients with baseline and 24-month VA measurements, mean VA decline was 6.1 letters in the worse-
seeing eye (n = 413) and 12.4 letters in the better-seeing eye (n = 414). The rate of progression to CNV in
either eye was 7.4% per patient-year.

CONCLUSIONS: At initial diagnosis, based on VA in the better-seeing eye, a high proportion of patients
with bilateral GA were ineligible to drive and approximately 7% were eligible for UK blindness registration.
The subsequent reduction in VA that occurred in the better-seeing eye would render a further two-thirds
ineligible to drive. These findings emphasize the severity of the visual disability associated with GA
secondary to AMD.

PMID: 29366564


Oral bisphosphonate use and age-related macular degeneration: retrospective cohort and nested
case-control study.
Garriga C, Pazianas M, Hawley S, Delmestri A, Prieto-Alhambra D, Cooper C, Judge A.

Abstract: Our objective here was to determine whether oral bisphosphonate (BP) use is associated with the incidence of age-related macular degeneration (AMD). We performed a population-based study using electronic health records from UK primary care (Clinical Practice Research Datalink). A cohort of 13,974 hip fracture patients (1999-2013) was used to conduct (1) a propensity score-matched cohort analysis and (2) a nested case-control analysis. Hip fracture patients were aged ≥50 years without AMD diagnosis before hip fracture date or in the first year of follow-up. Among 6208 matched patients and during 22,142 person-years of follow-up, 57 (1.8%) and 42 (1.4%) AMD cases occurred in BP users and non-BP users, respectively. The survival analysis model did not provide significant evidence of a higher risk of AMD in BP users (subhazard ratio: 1.60; 95% confidence interval (CI): 0.95-2.72; P = 0.08), although there was a significant increased risk among BP users with high medication possession ratio (MPR) (top quartile) relative to non-BP users (odds ratio: 5.08, 95% CI: 3.11-8.30; P < 0.001, respectively). Overall, oral BP use was not associated with an increased risk of AMD in this cohort of hip fracture patients, although the risk increased significantly with higher MPR. More data are needed to confirm these findings.

PMID: 29363763


The relationship between non-steroidal anti-inflammatory drug use and age-related macular degeneration.

Modjtahedi BS, Fong DS, Jorgenson E, Van Den Eeden SK, Quinn V, Slezak JS.

PURPOSE: To describe the relationship between the incidence of age-related macular degeneration (AMD) and non-steroidal anti-inflammatory drug (NSAIDs) use.

DESIGN: Prospective cohort study.

METHODS: This study consisted of participants in the California Men's Health Study. Those who completed surveys in 2002-2003 and 2006 were included. Men who self-reported use of aspirin, ibuprofen, naproxen, valdecoxib, celecoxib and/or rofecoxib at least three days per week were considered NSAID users. Patients were categorized as non-users, former users, new users, or longer-term users based on survey responses. NSAID use was also categorized by type: any NSAIDs, aspirin, and/or non-aspirin NSAIDs. Age, race/ethnicity, smoking status, education, income, alcohol use, and Charlson comorbidity index score were included in the multivariate analysis as risk factors for AMD.

RESULTS: 51,371 men were included. Average follow-up time was 7.4 years. There were 292 (0.6%) and 1,536 (3%) cases of exudative and non-exudative AMD, respectively. Longer-term use of any NSAID was associated with lower risk of exudative AMD (HR 0.69, 95% CI 0.50 - 0.96, p=0.029). New users of any NSAIDs (HR=0.79, 95% CI 0.68-0.93, p=0.0039) and aspirin (HR=0.82, 95% CI 0.70-0.97, p=0.018) had a lower risk of non-exudative AMD although this trend did not persist in longer-term users. The relationship between exudative or non-exudative AMD and the remaining categories of NSAID use were not significant.

CONCLUSION: The overall impact of NSAIDs on AMD incidence is small; however, the lower risk of exudative AMD in longer-term NSAID users may point to a protective effect and deserves further study as a possible mechanism to modulate disease risk.

PMID: 29360460
Stem cells

Regen Med. 2018 Jan 23. [Epub ahead of print]

Autologous stem cell therapy for inherited and acquired retinal disease.

Apatoff MBL, Sengillo JD, White EC, Bakhoun MF, Bassuk AG, Mahajan VB, Tsang SH.

Abstract: The mammalian retina, derived from neural ectoderm, has little regenerative potential. For conditions where irreversible retinal pigment epithelium or photoreceptor cell loss occurs, advanced techniques are required to restore vision. Inherited retinal dystrophies and some acquired conditions, such as age-related macular degeneration, have a similar end result of photoreceptor cell death leading to debilitating vision loss. These diseases stand to benefit from future regenerative medicine as dietary recommendations and current pharmacologic therapy only seek to prevent further disease progression. Cell-based strategies, such as autologously derived induced pluripotent stem cells, have come a long way in overcoming previous technical and ethical concerns. Clinical trials for such techniques are already underway. These trials and the preceding preclinical studies will be discussed in the context of retinal disease.

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A2E-associated cell death and inflammation in retinal pigmented epithelial cells from human induced pluripotent stem cells.

Parmar VM, Parmar T, Arai E, Perusek L, Maeda A.

Abstract: Accumulation of lipofuscin in the retinal pigmented epithelium (RPE) is observed in retinal degenerative diseases including Stargardt disease and age-related macular degeneration. Bis-retinoid N-retinyl-N-retinylidene ethanolamine (A2E) is a major component of lipofuscin. A2E has been implicated in RPE atrophy and retinal inflammation; however, mice with A2E accumulation display only a mild retinal phenotype. In the current study, human iPSC-RPE (hiPSC-RPE) cells were generated from healthy individuals to examine effects of A2E in human RPE cells. hiPSC-RPE cells displayed RPE-specific features, which include expression of RPE-specific genes, tight junction formation and ability to carry out phagocytosis. hiPSC-RPE cells demonstrated cell death and increased VEGF-A production in a time-dependent manner when they were cocultured with 10μM of A2E. PCR array analyses revealed upregulation of 26 and 12 pro-inflammatory cytokines upon A2E and H2O2 exposure respectively, indicating that A2E and H2O2 can cause inflammation in human retinas. Notably, identified gene profiles were different between A2E- and H2O2- treated hiPSC-RPE cells. A2E caused inflammatory changes observed in retinal degenerative diseases more closely as compared to H2O2. Collectively, these data obtained with hiPSC-RPE cells provide evidence that A2E plays an important role in pathogenesis of retinal degenerative diseases in humans.

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Diet, lifestyle & low vision


Therapeutic potential of omega-3 fatty acids supplementation in a mouse model of dry macular degeneration.

Correction: Therapeutic potential of omega-3 fatty acids supplementation in a mouse model of dry macular degeneration. [BMJ Open Ophthalmol. 2017]

PURPOSE: To evaluate the therapeutic effects of omega-3 (ω-3) and omega-6 (ω-6) fatty acids in the CCL2/- model of dry age-related macular degeneration (AMD). The blood level of eicosapentaenoic acid (EPA) and arachidonic acid (AA) served to adjust the treatment dosage (AA/EPA=1-1.5).

METHODS: Nine-month-old animals were allocated to different groups: (A) C57BL/6 untreated, (B) CCL2/- untreated, (C) CCL2/- treated with ω-3+ω-6, and (D) CCL2/- treated with ω-3. Treatment was daily administered by gavage for 3 months. Fatty acids analysis was performed and retinas were histologically examined. Three-month-old wild type mice were used for comparison purposes. Real-time PCR and Western blot were performed for retinal inflammatory mediators.

RESULTS: Increased EPA and decreased AA levels were observed in both blood and retinas in the treatment groups. The outer nuclear layer thickness was increased in groups C (45.0±3.9 µm) and D (62.8±4.9 µm), compared with groups B (65.6±3.0 µm) and A (71.1±4.2 µm), and in younger mice, it was 98.0±3.9 µm. A decrease in NF-κB expression was noted in the treatment groups. Interleukin (IL) 18 protein levels demonstrated a significant reduction in the ω-3-treated group only.

CONCLUSION: Supplementation with ω-3+ω-6 or ω-3 alone (AA/EPA=1-1.5) suggests a protective mechanism in the CCL2/- animal model of dry AMD, with a more beneficial effect when ω-3 are used alone. Our findings indicated that inflammation is not the only determining factor; perhaps a regenerative process might be involved following administration of ω-3 fatty acids.

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Correction: Therapeutic potential of omega-3 fatty acids supplementation in a mouse model of dry macular degeneration.[No authors listed]

Abstract: [This corrects the article DOI: 10.1136/bmjophth-2016-000056.][This corrects the article DOI: 10.1136/bmjophth-2016-000056.].

Erratum for: Therapeutic potential of omega-3 fatty acids supplementation in a mouse model of dry macular degeneration. [BMJ Open Ophthalmol. 2017]

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