Drug treatment

Eye (Lond). 2017 Jun 16. [Epub ahead of print]

Second-year visual acuity outcomes of nAMD patients treated with aflibercept: data analysis from the UK Aflibercept Users Group.

Almuhtaseb H, Johnston RL, Talks JS, Lotery AJ.

Purpose: To audit the visual acuity (VA) outcomes achieved at the end of year two in 17 UK centres, which followed the year 1 VIEW protocol in year 1, but a variable approach in year 2 for aflibercept for neovascular macular degeneration (nAMD).

Patients and methods: Retrospective data analysis, from an electronic medical record, of a consecutive series of treatment-naive nAMD patients who received aflibercept for 2 consecutive years, having followed the VIEW protocol in year one, defined as eyes having received 7 or 8 injections from baseline.

Results: The mean number of intravitreal injections (IVIs) during year 2 was 3.7 in 1180 eyes (1083 patients). The mean baseline VA of the whole cohort was 56.3 ETDRS letters, improving to 61.3 at 1 year (+5) and 59.1 (+2.8) at the end of year 2. The mean VA letter score at the end of year 2, stratified by number of IVIs into three groups was as follows: group A, 57.3 (gain of +1.7) (44% of eyes (<=3 IVIs)); group B, 59.8 (+3.8) (34% of eyes (4-5 IVIs)); group C, 61.7 (+3.7) (22% of eyes (>6 IVIs)). Even though there were VA gains in the three groups over the 2-years, there was a drop in VA in year one to two. Eyes that received >/=6 IVIs (group C) had a smaller reduction of VA during year 2 than those which received <3 IVIs (group A) (P=0.0014).

Conclusions: Providing a higher number of injections after a Q8 regime in year 1 results in higher VA gains in year 2 of treatment.

PMID: 28622328

Eye (Lond). 2017 Jun 16. [Epub ahead of print]

Identification of time point to best define ‘sub-optimal response’ following intravitreal ranibizumab therapy for diabetic macular edema based on real-life data.


Purpose: To determine the average time-point at which it is best to define ‘sub-optimal response’ after ranibizumab treatment for diabetic macular edema (DME) based on the data obtained from real-life clinical practice.

Methods: In this retrospective observational study, 322 consecutive treatment naïve eyes with DME were treated with three loading doses of intravitreal ranibizumab followed by re-treatment based on decision of...
the treating physician on a case-by-case basis. The demographic data, clinic-based visual acuity measurements and central subfield thickness (CST) assessed on spectral domain optical coherence tomography (OCT) were evaluated at baseline (month 0), 1, 2, 3, 6, and 12 months.

Results: On an average, the improvement in visual acuity and CST was first seen after the loading dose. However, the maximal response in terms of proportion of patients with improvement in visual acuity and/ or CST in this cohort was observed at 12 months. Patients who presented with low visual acuity at baseline (<37 ETDRS letters) were unlikely to attain driving vision with ranibizumab therapy.

Conclusions: On an average, a ‘sub-optimal response’ after ranibizumab therapy is best defined at month 12 as patients may continue to improve with treatment.

PMID: 28622321


Aqueous vascular endothelial growth factor and aflibercept concentrations after bimonthly intravitreal injections of aflibercept for age-related macular degeneration.

Sawada T, Wang X, Sawada O, Saishin Y, Ohji M.

IMPORTANCE: Clinical evidence supports the efficacy of bimonthly injection of aflibercept for age-related macular degeneration.

BACKGROUND: To evaluate aqueous vascular endothelial growth factor and aflibercept concentrations and the efficacy of bimonthly aflibercept injections in patients with age-related macular degeneration.

DESIGN A PROSPECTIVE, INTERVENTIONAL CASE SERIES:

PARTICIPANTS: Thirty-five eyes with exudative age-related macular degeneration.

METHODS: Patients received three bimonthly intravitreal aflibercept injections without loading doses. We collected the aqueous humor just before each injection, measured vascular endothelial growth factor and aflibercept concentrations by enzyme-linked immunosorbent assay, and measured best-corrected visual acuity and central retinal subfield thickness before and after the injections.

MAIN OUTCOME MEASURES: Vascular endothelial growth factor and aflibercept concentrations in the aqueous humor.

RESULTS: The vascular endothelial growth factor concentration was 135.4 ± 60.5 pg/ml (mean ± SD, range 60.6-323.4) at baseline and below the lowest detectable limit in all eyes at month 2 and in 32 eyes at month 4 (P<0.001 [month 2] and P<0.001 [month 4]). The mean aflibercept concentration was 20.3 ng/ml at month 2 and 28.0 ng/ml at month 4. The mean logarithm of the minimum angle of resolution visual acuity improved from 0.50 ± 0.36 at baseline to 0.36 ± 0.40 at month 6 (P<0.001). The mean central retinal subfield thickness decreased from 353 ± 100 μm at baseline to 236 ± 45 μm at month 6 (P<0.001).

CONCLUSIONS AND RELEVANCE: Bimonthly aflibercept injections without loading doses may be considered a treatment option for age-related macular degeneration.

PMID: 28621038


Ranibizumab versus dexamethasone implant for central retinal vein occlusion: the RANIDEX study.

Chatziralli I, Theodossiadis G, Kabanarou SA, Parikakis E, Xirou T, Mitropoulos P, Theodossiadis P.

PURPOSE: To compare intravitreal ranibizumab and dexamethasone implant in patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO).
METHODS: Participants were 42 treatment naive patients with ME due to CRVO, who received either intravitreal 0.5 mg ranibizumab (n = 25) or intravitreal 0.7 mg dexamethasone implant (n = 17). The main outcomes included the mean change in best corrected visual acuity (BCVA) and central subfield thickness (CST) at month 12 compared to baseline in the two groups.

RESULTS: At month 12, there was no statistically significant difference in BCVA and CST change between the two groups. However, there was recurrence in ME at month 5 in the dexamethasone group.

CONCLUSIONS: Both ranibizumab and dexamethasone implant were found to be safe and effective at the 12-month follow-up in patients with ME secondary to CRVO. Since there was a recurrence in ME at month 5 in the dexamethasone group, we suggested that intravitreal injection of dexamethasone implant should be potentially administered sooner than 6 months.

PMID: 28620704


Visual and Morphologic Outcomes in Eyes with Hard Exudate in the Comparison of Age-Related Macular Degeneration Treatments Trials.

Daniel E, Grunwald JE, Kim BJ, Maguire MG, Jaffe GJ, Toth CA, Ferris FL 3rd, Martin DF, Shaffer J, Ying GS; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group.

PURPOSE: To compare baseline characteristics, visual acuity (VA) and morphological outcomes between eyes with baseline hard exudates (HE) and all other eyes among patients with neovascular age-related macular degeneration (NVAMD) treated with anti-vascular endothelial growth factors (anti-VEGF).

DESIGN: Prospective cohort study within the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

PARTICIPANTS: Patients with NVAMD.

METHODS: Readers evaluated baseline and follow-up morphology on digital color images, fluorescein angiography (FA), and optical coherence tomography (OCT) in eyes with NVAMD that were randomly assigned to treatment with either ranibizumab or bevacizumab. Ophthalmologists identified HE on color images in the study eye.

MAIN OUTCOME MEASURES: VA; scar; geographic atrophy; retinal thickness, fluid; and number of anti-VEGF injections.

RESULTS: HE was present in 128 of 1185 (11%) study eyes at baseline, 77% within 1 disc diameter of the foveal center. Patients with study eye HE were more likely female (81% vs 60%; p=0.001) and non-smokers (53% vs 42%; p=0.004). Both groups had similar proportions of hypercholesterolemia and hypertriglyceridemia. At baseline, eyes with HE had worse VA (mean 57 vs 61 letters; p=0.003), larger total lesion size (3.3 vs 2.4 DA; p <0.001), greater total foveal thickness (522µm vs 452µm; p<0.001), more retinal angiomatous proliferation (18% vs 10%; p=0.009) and sub-RPE fluid (65% vs 47%; p<0.001). At 1 year, VA was similar in both groups, more eyes with baseline HE had no fluid (45% vs 29%; p<0.001) and greater reduction in total foveal thickness (-266µm vs -158µm; p<0.001). VA at year 2 was similar but retinas of eyes with baseline HE were thinner (267µm vs 299µm; p=0.03) and fewer eyes had sub-retinal fluid (23% vs 36%; p=0.008). HE was present in 19% of eyes at 1 year and 5% of eyes at 2 years. LIPC promoter SNP rs10468017 was not associated with NVAMD HE.

CONCLUSION: Eyes with HE have larger CNV lesions and more RAP. Their initially thicker retina rapidly becomes thinner on anti-VEGF treatment. HE is not significantly associated with hyperlipidemia. HE at baseline does not significantly influence VA, scar and GA outcomes in eyes with NVAMD treated with anti-VEGF. Few eyes have HE at year 2.

PMID: 28620652 PMCID: PMC5467458 [Available on 2018-01-01]
Effects of intravitreal injection of bevacizumab with or without anterior chamber paracentesis on intraocular pressure and peripapillary retinal nerve fiber layer thickness: a prospective study.

Soheilian M, Karimi S, Montahae T, Nikkhah H, Mosavi SA.

PURPOSE: To investigate the effects of intravitreal injection of bevacizumab (IVB) with or without anterior chamber paracentesis on intraocular pressure (IOP) and peripapillary retinal nerve fiber layer (PRNFL) thickness.

METHODS: In this prospective randomized clinical trial, 90 eyes with center involving diabetic macular edema or wet type age-related macular degeneration (AMD) were randomly assigned to receive IVB either without (group A) or with (group B) anterior chamber paracentesis. IOP was measured before and within 2 min, 30 min, 24 hours and 3 months after injections. Peripapillary spectral-domain optical coherence tomography (SD-OCT) was performed before and 3 months after injections.

RESULTS: Mean IOP changes 2 minutes, 30 minutes, 24 hours, and 3 months after injections were 26.4 ± 5.7 mmHg (P < 0.001), 6.5 ± 6.3 mmHg (P < 0.001), 0.2 ± 2.9 mmHg (P > 0.99) and 0.5 ± 2.4 mmHg (P > 0.99) in group A and -1.3 ± 2.4 mmHg (P < 0.001), -3.2 ± 1.8 mmHg (P < 0.001), -3.1 ± 1.8 mmHg (P < 0.001) and -1.8 ± 2.2 mmHg (P < 0.001) in group B, respectively. Mean baseline average PRNFL thickness was 85.3±5.6 μm and 85.6 ± 5 μm in groups A and B respectively. Mean PRNFL thickness changes after 3 month was -2 ± 2 μm (P < 0.001) in group A and 0 ± 2 μm (P = 0.101) in group B. Mean PRNFL thickness in group A decreased more than group B (P < 0.001).

CONCLUSION: Conventional method of IVB injection was associated with acute IOP rise and significant PRNFL loss 3 months after injection. Anterior chamber paracentesis prevents acute IOP rise and PRNFL loss.

PMID: 28616715

Comparison of Ranibizumab and Bevacizumab for Macular Edema Secondary to Retinal Vein Occlusions in Routine Clinical Practice.


BACKGROUND AND OBJECTIVE: To determine outcomes of intravitreal ranibizumab (IVR) (Lucentis; Genentech, South San Francisco, CA) versus bevacizumab (IVB) (Avastin; Genentech, South San Francisco, CA) for treatment of macular edema (ME) secondary to retinal vein occlusion (RVO) in routine clinical practice.

PATIENTS AND METHODS: A retrospective study identified treatment-naïve patients with ME secondary to RVO where treatment with either IVB or IVR was initiated. Retreatment criteria were based on ophthalmic examination and/or spectral-domain optical coherence tomography findings.

RESULTS: Central RVO/hemi-RVO cohort: At 12 months, change in visual acuity (VA) (IVR: +12.9 letters, IVB +6.9 letters; P = .53), central subfield thickness (CST) (IVR: -144.1 μm, IVB: -153.9 μm; P = .88), and number of injections (IVR: 5.40 injections, IVB: 5.64 injections; P = .70) were not different between groups. Branch RVO cohort: At 12-month follow-up, no differences in change in VA (IVR: +15.2 letters, IVB: +10.6 letters; P = .46), CST (IVR: -23.1 μm, IVB: -91.4 μm; P = .16), or number of injections (IVR: 5.93 injections, IVB: 5.13 injections; P = .15) were noted.

CONCLUSION: There is no notable difference in outcome between IVR and IVB when treating ME from RVO in routine clinical practice. [Ophthalmic Surg Lasers Imaging Retina. 2017;48:465-472.].

PMID: 28613352
CLINICOPATHOLOGIC CORRELATION OF RETINAL ANGIOMATOUS PROLIFERATION TREATED WITH RANIBIZUMAB.

Skalet AH, Miller AK, Klein ML, Lauer AK, Wilson DJ.

PURPOSE: To describe histopathologic features of an eye with retinal angiomatous proliferation (RAP) secondary to age-related macular degeneration treated with serial ranibizumab injections and to correlate these findings with spectral domain optical coherence tomography.

METHODS: Histopathologic features from serial sections through the globe of a 93-year-old man with age-related macular degeneration were studied and compared with spectral domain optical coherence tomography images obtained 7 weeks before his death.

RESULTS: The pathologic correlate of ranibizumab-treated RAP was a circumscribed, branching paucicellular vascular complex extending from the inner plexiform layer to Bruch membrane. The histopathologic findings corresponded to an area of hyperreflectivity on spectral domain optical coherence tomography imaging, substantiating the reported tomographic appearance of RAP lesions. A frank anastomosis with choroidal or retinal vasculature was not seen in this treated RAP lesion. There was a lack of retinal pigment epithelium underlying the lesion in an area of retinal pigment epithelium detachment. The elastic portion of Bruch membrane appeared intact. Treatment with ranibizumab over an extended period of time may have been associated with a loss of cellularity of the RAP lesion.

CONCLUSION: In a patient with ARMd extensively treated with ranibizumab, color fundus photography, fluorescein angiography and SD-OCT images of RAP correlated histopathologically with a paucicellular intraretinal vascular complex.

PMID: 28613221

OPTICAL COHERENCE TOMOGRAPHY BASELINE PREDICTORS FOR INITIAL BEST-CORRECTED VISUAL ACUITY RESPONSE TO INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT IN EYES WITH DIABETIC MACULAR EDEMA: The CHARTRES Study.

Santos AR, Costa MÂ, Schwartz C, Alves D, Figueira J, Silva R, Cunha-Vaz JG.

PURPOSE: To identify baseline optical coherence tomography morphologic characteristics predicting the visual response to anti-vascular endothelial growth factor therapy in diabetic macular edema.

METHODS: Sixty-seven patients with diabetic macular edema completed a prospective, observational study (NCT01947881-CHARTRES). All patients received monthly intravitreal injections of Lucentis for 3 months followed by PRN treatment and underwent best-corrected visual acuity measurements and spectral domain optical coherence tomography at Baseline, Months 1, 2, 3, and 6. Visual treatment response was characterized as good (≥10 letters), moderate (5-10 letters), and poor (<5 or letters loss). Spectral domain optical coherence tomography images were graded before and after treatment by a certified Reading Center.

RESULTS: One month after loading dose, 26 patients (38.80%) were identified as good responders, 19 (28.35%) as Moderate and 22 (32.83%) as poor responders. There were no significant best-corrected visual acuity and central retinal thickness differences at baseline (P = 0.176; P = 0.573, respectively). Ellipsoid zone disruption and disorganization of retinal inner layers were good predictors for treatment response, representing a significant risk for poor visual recovery to anti-vascular endothelial growth factor therapy (odds ratio = 10.96; P < 0.001 for ellipsoid zone disruption and odds ratio = 7.05; P = 0.034 for disorganization of retinal inner layers).

CONCLUSION: Damage of ellipsoid zone, higher values of disorganization of retinal inner layers, and
central retinal thickness decrease are good predictors of best-corrected visual acuity response to antivascular endothelial growth factor therapy.

PMID: 28613220


Correlation between short- and long-term effects of intravitreal ranibizumab therapy on macular edema after branch retinal vein occlusion: a prospective observational study.

Minami Y, Nagaoka T, Ishibazawa A, Yoshida A.

BACKGROUND: The correlation between the short- and long-term effects of intravitreal ranibizumab (IVR) on macular edema after branch retinal vein occlusion (BRVO) remains unclear. We assessed the correlation between the short- and long-term effects of IVR on macular edema after BRVO.

METHODS: Twenty-one eyes with macular edema after BRVO were enrolled in this prospective observational study. We measured the foveal thickness (FT) and the best-corrected visual acuity (BCVA) before, 1 day after, and 1 month after IVR (0.5 mg) and then at least every 2 months thereafter until 6 months after the injection. If the macular edema recurred, another injection was administered. The primary endpoint was the change from baseline in the BCVA (ΔVA).

RESULTS: The mean logarithm of the minimum angle of resolution VA improved significantly (p = 0.01, p < 0.0001, respectively) after 1 day from 0.65 ± 0.28 to 0.51 ± 0.21 (20/89 to 20/63, Snellen equivalent) and after 6 months to 0.29 ± 0.24 (20/39, Snellen equivalent). The mean FT decreased significantly (p < 0.0001) after 1 day from 482 ± 85 μm to 349 ± 75 μm and after 6 months to 305 ± 84 μm. The 1-day VA was significantly (r = 0.68, p = 0.0007) positively correlated with the 6-month VA. The 1-day ΔVA was significantly (r = 0.79, p < 0.0001) positively correlated with the 6-month ΔVA.

CONCLUSIONS: The short-term effects of IVR may predict the long-term effects of IVR in macular edema secondary to BRVO.

PMID: 28610573 PMCID: PMC5470248

Retina. 2017 Jun 9. [Epub ahead of print]

HIGH-DOSE HIGH-FREQUENCY AFLIBERCEPT FOR RECALCITRANT NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

You QS, Gaber R, Meshi A, Ramkumar HL, Alam M, Muftuoglu IK, Freeman WR.

PURPOSE: To determine the efficacy of monthly (0.1 mL/4 mg) aflibercept for refractory neovascular age-related macular degeneration (wet age-related macular degeneration).

METHODS: This was a retrospective interventional case series in which patients with wet age-related macular degeneration were treated with stepwise dose escalation. Nonvitrectomized patients resistant to monthly (Q4W) ranibizumab/bevacizumab were switched to 2 mg aflibercept every 8 weeks. With resistance, they were escalated to Q4W 2 mg aflibercept, then Q4W 4 mg (high dose high frequency, 4Q4W) aflibercept. Resistance was defined as ≥2 recurrences after being dry following ≥3 injections or persistent exudation on treatment of ≥5 injections.

RESULTS: Thirty-three eyes of 28 patients were treated with 4Q4W aflibercept and followed for a mean of 16 months. A dry retina (no intraretinal or subretinal fluid) was achieved after initiating 4Q4W aflibercept treatment at a mean of 3.8 months. Central foveal thickness, maximum foveal thickness, intraretinal fluid, subretinal fluid, and retinal pigment detachment height decreased significantly at 1 month after initiating the 4Q4W aflibercept, and the morphologic therapeutic effect was sustained until the last visit. Forty-five
percent of eyes had one or more lines of vision improvement. New geographic atrophy developed in 9% of eyes during follow-up. No ocular or systemic adverse events occurred after initiating 4Q4W aflibercept.

CONCLUSION: Intravitreal high-dose high-frequency aflibercept is an effective treatment for patients with refractory wet age-related macular degeneration. 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: 28604541

Ophthalmologica. 2017 Jun 10. [Epub ahead of print]

Comparative Retinal Vessel Size Study of Intravitreal Ranibizumab and Bevacizumab in Eyes with Neovascular Age-Related Macular Degeneration.

Kurt MM, Çekiç O, Akpolat Ç, Aslankurt M, Elcioğlu MN.

PURPOSE: The aim of this paper was to assess and compare the effects of intravitreal ranibizumab and bevacizumab on retinal vessel diameter in eyes with neovascular age-related macular degeneration (AMD).

METHODS: Patients with neovascular AMD who underwent intravitreal injection of either ranibizumab or bevacizumab were included. Noninjected fellow eyes served as a control. The main outcome measures were central retinal artery equivalent (CRAE), central retinal vein equivalent (CRVE), and the artery-vein ratio (AVR).

RESULTS: In the ranibizumab group, the mean CRAE value decreased significantly at 1 week and 1 month (p = 0.002). The AVR value decreased significantly at 1 month (p = 0.028). CRVE values did not change at 1 week and 1 month (p = 0.083). In the bevacizumab group, the preinjection CRAE, CRVE, and AVR values did not change through the study period (p = 0.128, p = 0.600, and p = 0.734, respectively).

CONCLUSION: These results suggest that intravitreal ranibizumab led to significant retinal arteriolar vasoconstriction in eyes with neovascular AMD.

PMID: 28601887


Full-thickness macular hole formation following anti-VEGF injections for neovascular age-related macular degeneration.

Kabanarou SA, Xirou T, Mangouritsas G, Garnavou-Xirou C, Boutouri E, Gkizis I, Chatziralli I.

PURPOSE: Macular hole (MH) is part of a group of age-related degenerative diseases characterized by pathology of vitreomacular interface. Similarly, neovascular age-related macular degeneration (nAMD) affects older patients and is a leading cause of irreversible visual loss. The purpose of this case series is to describe the development of full-thickness MH in patients with nAMD, following antivascular endothelial growth factor (anti-VEGF) treatment.

METHODS: Participants in this case series were four patients with nAMD, who received anti-VEGF injections with variable therapeutic response to treatment. Patients were examined at baseline (when AMD was diagnosed) and monthly thereafter. The examination included visual acuity measurement, slit-lamp biomicroscopy, and optical coherence tomography.

RESULTS: All patients were found to develop full-thickness MH within 1-4 months after the last anti-VEGF injection, even in the absence of pre-existing vitreomacular interface abnormalities in some cases. The median number of injections before the MH formation was 3.
CONCLUSION: MH formation may represent an adverse effect of anti-VEGF treatment in patients with nAMD and could be also coexisting pathology with nAMD in older individuals.

PMID: 28603410 PMCID: PMC5457126

Eye (Lond). 2017 Jun 16. [Epub ahead of print]

Clinical real-world results of switching treatment from ranibizumab to aflibercept in patients with diabetic macular oedema.


PMID: 28622326


Anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration: Comparison of Age-related Macular Degeneration Treatments Trials 5 year outcomes and implication for clinical practice.

Chong EW, Al-Qureshi SH.

PMID: 28618455

Other treatment & diagnosis

Retina. 2017 Jan 23. [Epub ahead of print]

MACULAR DEGENERATION AND ASPIRIN USE.

Small KW, Garabetian CA, Shaya FS.

PURPOSE: To review current literature of the benefits that aspirin provides for patients' cardiovascular health compared with the risk of AMD worsening.

METHODS: We performed a review and critically analyzed six cardiovascular and four ophthalmological trials regarding risks and benefits of aspirin use. The prospective randomized cardiovascular trials had a cumulative 167,580 while the 3 smaller ophthalmological data sets had a cumulative 12,015 subjects.

RESULTS: The reviewed meta-analysis literature demonstrated a statistically significant 32% reduction in the risk of nonfatal stroke with regular aspirin users. The study also documented that aspirin users decreased the risk of fatal vascular deaths by 15%. Of the three ophthalmological studies highlighting the adverse affects of aspirin association with AMD, all suggested an exacerbation of AMD without statistical significance and broad confidence bands.

CONCLUSION: Overall, the number, size, and quality of the cardiovascular studies recommending aspirin use are far superior to the fewer, smaller and conflicting studies suggesting a possible adverse effect of aspirin use in relation to AMD. The benefits of aspirin usage include preserving the duration and quality of life by decreasing stroke and heart attack risk. These benefits seem to far outweigh the theoretical risks of possibly exacerbating wet AMD, which can be reasonably controlled with anti-VEGF therapy.

PMID: 28613225
**Pathogenesis**


The link between morphology and complement in ocular disease.

Mohlin C, Sandholm K, Ekdahl KN, Nilsson B.

Abstract: The complement system is a vital component of the immune-privileged human eye that is always active at a low-grade level, preventing harmful intraocular injuries caused by accumulation of turnover products and controlling pathogen to preserve eye homeostasis and vision. The complement system is a double-edged sword that is essential for protection but may also become harmful and contribute to eye pathology. Here, we review the evidence for the involvement of complement system dysregulation in age-related macular degeneration, glaucoma, uveitis, and neuromyelitis optica, highlighting the relationship between morphological changes and complement system protein expression and regulation in these diseases. The potential benefits of complement inhibition in age-related macular degeneration, glaucoma, uveitis, and neuromyelitis optica are abundant, as are those of further research to improve our understanding of complement-mediated injury in these diseases.

PMID: 28622910


Mutant Fibulin-3 Causes Proteoglycan Accumulation and Impaired Diffusion Across Bruch's Membrane.

Zayas-Santiago A, Cross SD, Stanton JB, Marmorstein AD, Marmorstein LY.

PURPOSE: The mutation R345W in EFEMP1 (fibulin-3) causes macular degeneration. This study sought to determine whether proteoglycan content and diffusion across Bruch's membrane are altered in Efemp1ki/ki mice carrying this mutation or in Efemp1-/- mice.

METHODS: Proteoglycans in mouse Bruch's membranes were stained with Cupromeronic Blue (CB). Heparan sulfated proteoglycan (HSPG) and chondroitin/dermatan sulfate proteoglycan (C/DSPG) distributions were visualized following treatments with chondroitinase ABC (C-ABC) or nitrous acid. Total sulfated glycosaminoglycans (sGAGs) in Bruch's membrane/choroid (BrM/Ch) were measured with dimethylmethylene blue (DMMB). Matrix metalloprotease (MMP)-2, MMP-9, and tissue inhibitor of metalloproteinase (TIMP)-3 were examined by immunofluorescence and quantified using Image J. Molecules with different Stokes radius (Rs) were allowed simultaneously to diffuse through mouse BrM/Ch mounted in a modified Ussing chamber. Samples were quantified using gel exclusion chromatography.

RESULTS: HSPGs and C/DSPGs were markedly increased in Efemp1ki/ki Bruch's membrane, and MMP-2 and MMP-9 were decreased, but TIMP-3 was increased. Diffusion across Efemp1ki/ki Bruch's membrane was impaired. In contrast, the proteoglycan amount in Efemp1-/- Bruch's membrane was not significantly different, but the size of proteoglycans was much larger. MMP-2, MMP-3, and TIMP-3 levels were similar to that of Efemp1+/+ mice, but they were localized diffusely in retinal pigment epithelium (RPE) cells instead of Bruch's membrane. Diffusion across Efemp1-/- Bruch's membrane was enhanced.

CONCLUSIONS: Mutant fibulin-3 causes proteoglycan accumulation, reduction of MMP-2 and MMP-9, but increase of TIMP-3, and impairs diffusion across Bruch's membrane. Fibulin-3 ablation results in altered sizes of proteoglycans, altered distributions of MMP-2, MMP-9, and TIMP-3, and enhances diffusion across Bruch's membrane.

PMID: 28622396

Discovery of highly potent and selective small-molecule reversible Factor D inhibitors demonstrating alternative complement pathway inhibition in vivo.


Abstract: The highly specific S1 serine protease Factor D (FD) plays a central role in the amplification of the complement alternative pathway (AP) of the innate immune system. Genetic associations in humans have implicated AP activation in age-related macular degeneration (AMD), and AP dysfunction predisposes individuals to disorders such as paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). The combination of structure-based hit identification and subsequent optimization of the center (S)-proline-based lead 7 has led to the discovery of non-covalent reversible and selective human Factor D (FD) inhibitors with drug-like properties. The orally bioavailable compound 2 exerted excellent potency in 50% human whole blood in vitro and blocked AP activity ex vivo after oral administration to monkeys as demonstrated by inhibition of membrane attack complex (MAC) formation. Inhibitor 2 demonstrated sustained oral and ocular efficacy in a model of lipopolysaccharide (LPS)-induced systemic AP activation in mice expressing human FD.

PMID: 28621538


Molecular mechanisms of signaling via the docosanoid neuroprotectin D1 for cellular homeostasis and neuroprotection.

Asatryan A, Bazan NG.

Abstract: Docosahexaenoic acid (DHA), an omega-3 essential fatty acid family member that is enriched in the nervous system, generates bioactive docosanoids that can counteract disruptions of cellular homeostasis. Docosanoids include neuroprotectin D1 (NPD1), which is decreased in the CA1 hippocampal area of patients with early-stage Alzheimer's disease (AD). We summarize here how NPD1 elicits neuroprotection by up-regulating c-REL, a nuclear factor (NF)-kappaB subtype that, in turn, enhances expression of BIRC3 (baculoviral IAP repeat-containing protein 3, or cIAP2) in retinal cells. This DHA/NPD1-inducible pathway also is activated in an experimental ischemic stroke model and leads to neurological protection. Further elucidating the mechanisms of action of NPD1 and other docosanoids will contribute to managing diseases, including stroke, AD, age-related macular degeneration, traumatic brain injury, Parkinson's disease, and other neurodegenerative diseases.

PMID: 28615451


Microfluidic co-cultures of retinal pigment epithelial cells and vascular endothelial cells to investigate choroidal angiogenesis.

Chen LJ, Ito S, Kai H, Nagamine K, Nagai N, Nishizawa M, Abe T, Kaji H.

Abstract: Angiogenesis plays a critical role in many diseases, including macular degeneration. At present, the pathological mechanisms remain unclear while appropriate models dissecting regulation of angiogenic processes are lacking. We propose an in vitro angiogenesis process and test it by examining the co-culture of human retinal pigment epithelial cells (ARPE-19) and human umbilical vein endothelial cells (HUVEC) inside a microfluidic device. From characterisation of the APRE-19 monoculture, the tight junction protein (ZO-1) was found on the cells cultured in the microfluidic device but changes in the medium conditions did
not affect the integrity of monolayers found in the permeability tests. Vascular endothelial growth factor (VEGF) secretion was elevated under low glucose and hypoxia conditions compared to the control. After confirming the angiogenic ability of HUVEC, the cell-cell interactions were analyzed under lowered glucose medium and chemical hypoxia by exposing ARPE-19 cells to cobalt (II) chloride (CoCl2). Heterotypic interactions between ARPE-19 and HUVEC were observed, but proliferation of HUVEC was hindered once the monolayer of ARPE-19 started breaking down. The above characterisations showed that alterations in glucose concentration and/or oxygen level as induced by chemical hypoxia causes elevations in VEGF produced in ARPE-19 which in turn affected directional growth of HUVEC.

PMID: 28615726 PMCID: PMC5471206


Amyloid β peptides overexpression in retinal pigment epithelial cells via AAV-mediated gene transfer mimics AMD-like pathology in mice.

Prasad T, Zhu P, Verma A, Chakraborty P, Rosario AM, Golde TE, Li Q.

Abstract: Age-related macular degeneration (AMD) is a progressive retinal neurodegenerative disorder characterized by extracellular deposits known as drusen. A major constituent of drusen deposits are Alzheimer disease-associated amyloid β (Aβ) peptides. To understand the etiology of Aβ proteostasis in AMD, we delivered recombinant adeno-associated virus (AAV) encoding Aβ42 and Aβ40 peptides fused to BRI2 protein by intraocular injection in C57BL/6J mice. Endogenous protease cleavage of such constructs leads to production of secreted Aβ42 and Aβ40 respectively. We demonstrate that overexpression of secreted Aβ40 or Aβ42 resulted in dramatic induction of drusen-like deposits by 2 months' post-injection. These drusen-like deposits were immunopositive for Aβ and complement proteins but did not stain for conventional amyloid dyes, such as Thioflavin S. Both injected cohorts showed gliosis and degenerative changes, though ERG responses were minimally affected. Intriguingly, simultaneous overexpression of BRI-Aβ40 or BRI-Aβ42 together resulted in dose-dependent and cumulative changes reminiscent of AMD type pathology - drusen-like deposits, severe reduction in ERG responses, photoreceptor cell loss and gliosis. Here, we have established a physiological model of Aβ containing deposits in wild-type mice that recapitulates major retinal pathophysiological features of AMD and will be instrumental in mechanistic understanding and development of therapeautic strategies against AMD.

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Retinal Macrophages Synthesize C3 and Activate Complement in AMD and in Models of Focal Retinal Degeneration.


PURPOSE: Complement system dysregulation is strongly linked to the progression of age-related macular degeneration (AMD). Deposition of complement including C3 within the lesions in atrophic AMD is thought to contribute to lesion growth, although the contribution of local cellular sources remains unclear. We investigated the role of retinal microglia and macrophages in complement activation within atrophic lesions, in AMD and in models of focal retinal degeneration.

METHODS: Human AMD donor retinas were labeled for C3 expression via in situ hybridization. Rats were subject to photo-oxidative damage, and lesion expansion was tracked over a 2-month period using optical coherence tomography (OCT). Three strategies were used to determine the contribution of local and systemic C3 in mice: total C3 genetic ablation, local C3 inhibition using intravitreally injected small interfering RNA (siRNA), and depletion of serum C3 using cobra venom factor.

RESULTS: Retinal C3 was expressed by microglia/macrophages located in the outer retina in AMD eyes.
In rodent photo-oxidative damage, C3-expressing microglia/macrophages and complement activation were located in regions of lesion expansion in the outer retina over 2 months. Total genetic ablation of C3 ameliorated degeneration and complement activation in retinas following damage, although systemic depletion of serum complement had no effect. In contrast, local suppression of C3 expression using siRNA inhibited complement activation and deposition, and reduced cell death.

CONCLUSIONS: These findings implicate C3, produced locally by retinal microglia/macrophages, as contributing causally to retinal degeneration. Consequently, this suggests that C3-targeted gene therapy may prove valuable in slowing the progression of AMD.

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**Prog Retin Eye Res. 2017 Jun 7. [Epub ahead of print]**

**On phagocytes and macular degeneration.**


Abstract: Age related macular degeneration (AMD) is a complex multifactorial disease caused by the interplay of age and genetic and environmental risk factors. A common feature observed in early and both forms of late AMD is the breakdown of the physiologically immunosuppressive subretinal environment and the protracted accumulation of mononuclear phagocytes (MP). We here discuss the origin and nature of subretinal MPs, the mechanisms that lead to their accumulation, the inflammatory mediators they produce as well as the consequences of their chronic presence on photoreceptors, retinal pigment epithelium and choroid. Recent advances highlight how both genetic and environmental risk factors directly promote subretinal inflammation and tip the balance from a beneficial inflammation that helps control debris accumulation to detrimental chronic inflammation and destructive late AMD. Finally, we discuss how changes in life style or pharmacological intervention can help to break the vicious cycle of inflammation and degeneration, restore the immunosuppressive properties of the subretinal space, and reestablish homeostasis.

PMID: 28602950

**Vision Res. 2017 Jun 7. [Epub ahead of print]**

**VEGF production and signaling in Müller glia are critical to modulating vascular function and neuronal integrity in diabetic retinopathy and hypoxic retinal vascular diseases.**

Le YZ.

Abstract: Müller glia (MG) are major retinal supporting cells that participate in retinal metabolism, function, maintenance, and protection. During the pathogenesis of diabetic retinopathy (DR), a neurovascular disease and a leading cause of blindness, MG modulate vascular function and neuronal integrity by regulating the production of angiogenic and trophic factors. In this article, I will (1) briefly summarize our work on delineating the role and mechanism of MG-modulated vascular function through the production of vascular endothelial growth factor (VEGF) and on investigating VEGF signaling-mediated MG viability and neural protection in diabetic animal models, (2) explore the relationship among VEGF and neurotrophins in protecting Müller cells in in vitro models of diabetes and hypoxia and its potential implication to neuroprotection in DR and hypoxic retinal diseases, 7and (3) discuss the relevance of our work to the effectiveness and safety of long-term anti-VEGF therapies, a widely used strategy to combat DR, diabetic macular edema, neovascular age-related macular degeneration, retinopathy of prematurity, and other hypoxic retinal vascular disorders.

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Epidemiology


The Association between Age-Related Macular Degeneration and the Risk of Mortality.

Wang P, Wang J, Ma J, Jin G, Guan X.

Abstract: Studies have investigated the association between age-related macular degeneration (AMD) and subsequent risks of mortality, but results have been equivocal. We conducted a comprehensive analysis of prospective cohort studies to assess the association of AMD and the risk of mortality in the general population. We searched PubMed and EMBASE for trials published from 1980 to 2016. We included 11 cohort studies that reported relative risks with 95% confidence intervals for the association of AMD and mortality, involving 57,069 participants. In a random-effects model, the adjusted RR (95% confidence interval) associated with AMD was 1.09 (1.02-1.17) for all-cause mortality. Findings from this research provide support that persons with AMD had a higher subsequent risk of mortality than persons without AMD.

PMID: 28607930 PMCID: PMC5451765


AIMS: To assess the burden of vision loss due to eye disease in China between 1990 and 2015, and to predict the burden in 2020.

METHODS: Data from the GBD 2015 (Global Burden of Diseases, Injuries, and Risk Factors Study 2015) were used. The main outcome measures were prevalence and years lived with disability (YLDs) for vision loss due to cataract, glaucoma, macular degeneration, other vision loss, refraction and accommodation disorders and trachoma.

RESULTS: Prevalence for eye diseases increased steadily from 1990 to 2015, and will increase until 2020. From 1990 to 2015, the most common eye disorder was refraction and accommodation disorders. From 1990 to 2015, the vision loss burden due to eye disease decreased for those aged 0-14 years, and increased for those aged 15 years and above, with the most notable increases occurring among those aged 50 years and above. China ranked 10th when comparing YLDs for vision loss due to eye disease with the other members of the G20 (Group of Twenty, an international forum for the governments from 20 major economies). Age-standardised YLD rates for vision loss due to eye disease declined in all 19 countries, except for China. The burden from vision loss due to eye disease ranked 12th and 11th among all causes of health loss in China in 1990 and 2015, respectively.

CONCLUSION: Alone among major economies, China has experienced an increase in the burden of age-standardised vision loss from eye disease over the last two decades. In the future, China may expect a growing burden of vision loss due to population growth and ageing.

PMID: 28607177

Diet, lifestyle & low vision

Ophthalmology. 2017 Jun 8. [Epub ahead of print]

Decreased Visual Function Scores on a Low Luminance Questionnaire Is Associated with Impaired
**Dark Adaptation.**


PURPOSE: We investigate whether responses on a Low Luminance Questionnaire (LLQ) in patients with a range of age-related macular degeneration (AMD) severity are associated with their performance on focal dark adaptation (DA) testing and with choroidal thickness.

DESIGN: Cross-sectional, single-center, observational study.

PARTICIPANTS: A total of 113 participants older than 50 years of age with a range of AMD severity.

METHODS: Participants answered the LLQ on the same day they underwent DA testing using a focal dark adaptometer measuring rod intercept time (RIT). We performed univariable and multivariable analyses of the LLQ scores and age, RIT, AMD severity, subfoveal choroidal thickness [SFCT], phakic status, and best-corrected visual acuity.

MAIN OUTCOME MEASURES: The primary outcome of this study was the score on the 32-question LLQ. Each item in the LLQ is designated to 1 of 6 subscales describing functional problems in low luminance: driving, emotional distress, mobility, extreme lighting, peripheral vision, and general dim lighting. Scores were computed for each subscale, in addition to a weighted total mean score.

RESULTS: Responses from 113 participants (mean age, 76.2±9.3 years; 58.4% were female) and 113 study eyes were analyzed. Univariable analysis demonstrated that lower scores on all LLQ subscales were correlated with prolonged DA testing (longer RIT) and decreased choroidal thickness. All associations were statistically significant except for the association of choroidal thickness and "peripheral vision." The strongest association was the LLQ subscale of driving with RIT (r = -0.97, P < 0.001). Multivariable analysis for each of the LLQ subscale outcomes, adjusted for age, included RIT, with total LLQ score, "driving," "extreme lighting," and "mobility" also including choroidal thickness. In all multivariable analyses, RIT had a stronger association than choroidal thickness.

CONCLUSIONS: This cross-sectional analysis demonstrates associations of patient-reported functional deficits, as assessed on the LLQ, with both reduced DA and reduced choroidal thickness, in a population of older adults with varying degrees of AMD severity and good visual acuity in at least 1 eye. These analyses suggest that local functional measurements of DA testing (RIT) and choroidal thickness are associated with patient-reported functional deficits.

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