Type 3 neovascularisation (retinal angiomatous proliferation) treated with antivascular endothelial growth factor: real-world outcomes at 24 months.

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Aims: To compare 24 months outcomes of eyes with retinal angiomatous proliferations (RAPs) treated with antivascular endothelial growth factor (anti-VEGF) with a group of controls diagnosed with other neovascular age-related macular degeneration (nAMD) subtypes in a real-world setting.

Methods: Treatment-naïve nAMD eyes that commenced anti-VEGF between January 2006 and November 2015 were identified from a registry of nAMD treatment outcomes. Cases were defined as eyes diagnosed with RAP. Three controls per case were selected among nAMD eyes with non-RAP lesions and matched on baseline visual acuity (VA), year of treatment initiation, anti-VEGF agent first injected and follow-up. Baseline VA was compared with 12 and 24 months VA. Change in VA, number of injections received, proportion of visits with active nAMD and time to first inactivation were compared between RAPs and controls.

Results: 157 RAPs and 469 controls were included. Baseline VA (mean (SD)) increased at 12 months (61.4 (15.5) vs 68.7 (14.7) letters, p<0.001) and remained higher (66.6 (17.3) letters) at 24 months (p<0.001) in RAPs. The change from baseline VA (mean(95% CI)) was significantly higher in RAPs than in controls at 12 months (7.3 (5.4 to 9.1) vs 4.1 (2.8 to 5.4) letters, p=0.01) and at 24 months (5.1 (2.8 to 7.3) vs 2.5 (1 to 4) letters, p=0.056). Both groups received a median of 13 injections. RAPs inactivated earlier and were less active than controls (both p<0.001).

Conclusions: RAPs responded well to anti-VEGF, with a significant improvement in VA persisting at 24 months. RAPs had better visual outcomes than controls at 12 and 24 months, tended to inactivate earlier and were less active throughout 2 years follow-up.

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Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat and extend regimen: FLUID study 24 month results.

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**Purpose:** To test the hypothesis that tolerating some subretinal fluid (SRF) in patients with neovascular age-related macular degeneration (nAMD) treated with ranibizumab using a treat-and-extend (T&E) regimen can achieve similar visual acuity (VA) outcomes as treatment aimed at resolving all SRF.

**Design:** Multi-center, randomized, 24-month, phase IV, single-masked, non-inferiority clinical trial.

**Subjects:** Subjects presenting with treatment-naive nAMD.

**Intervention:** Subjects with active subfoveal choroidal neovascularization (CNV) were randomized to receive ranibizumab 0.5 mg monthly until either complete resolution of SRF and intraretinal fluid (IRF) (intensive arm: SRF intolerant) or resolution of all IRF only (relaxed arm: SRF tolerant except for SRF >200 μm at the foveal centre) before extending treatment intervals. A 5-letter non-inferiority margin was applied to the primary outcome measure.

**Main Outcome Measures:** Mean change in best-corrected visual acuity (BCVA), mean change in central subfield thickness (CST) and number of ranibizumab injections from baseline to month 24.

**Results:** Of the 349 subjects randomized (intensive: 174; relaxed: 175), 279 (79.9%) completed the month 24 visit. Baseline characteristics were well balanced except area of lesion and area of CNV. The mean (SD) change in BCVA from baseline to month 24 was 3.0 (16.3) letters in the intensive group and 2.6 (16.3) letters in the relaxed group, demonstrating non-inferiority of the relaxed to the intensive treatment (P=0.99). Similar proportions of the intensive and relaxed groups achieved ≥20/40 VA (53.5% and 56.6%, respectively; P=0.92) and ≤20/200 VA (8.7% and 8.1%, respectively; P=0.52). Results were supported by the per protocol analysis and adjustment for confounding baseline factors. Subjects in the relaxed group received fewer ranibizumab injections over 24 months (mean [SD]; 15.8 [5.9]) than those in the intensive group (17 [6.5]; p=0.001). Significantly more subjects in the intensive group never extended beyond 4-weekly treatment intervals (13.5%) than in the relaxed group (2.8%; p=0.003) and significantly more subjects in the relaxed group extended to and maintained 12-weekly treatment intervals (29.6%) than the intensive group (15.0%; p=0.005).

**Conclusions:** Patients treated with a ranibizumab T&E protocol that tolerated some SRF achieved VA that is comparable, with fewer injections, to that achieved when treatment aimed to completely resolve all SRF.

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Better visual outcome at 1 year with antivascular endothelial growth factor treatment according to treat-and-extend compared with pro re nata in eyes with neovascular age-related macular degeneration.


**Purpose:** To evaluate treatment outcome at 12 months in eyes with neovascular age-related macular degeneration (nAMD) treated with antivascular endothelial growth factor (anti-VEGF) injections according to either pro re nata (PRN)- or treat-and-extend (TE)-regimen in one clinical setting in Sweden.

**Methods:** Data were obtained retrospectively from the Swedish Macula Register, optical coherence tomography-database and electronic patient charts. The study included 443 eyes; 223 PRN- and 220 TE-treated eyes. Baseline (BL) characteristics and follow-up data at 6 and 12 months were collected. Statistical regression analysis was performed to evaluate association between treatment strategy and visual outcome at 12 months.
Results: Baseline (BL) characteristics were well balanced between cohorts. Visual acuity at 12 months was higher in TE-cohort 66.5 (13.1) compared to PRN-cohort 60.1 (17.6) (p = 0.000). Visual improvement at 12 months was +5.2 (11.8) and +1.2 (12.7) letters Early Treatment Diabetic Retinopathy Study (ETDRS) in TE- and PRN-cohorts, respectively (p = 0.002). Number of administered injections at 12 months was 10.2 (2.1) and 6.3 (2.1) in the two cohorts (p = 0.000). Statistical analysis demonstrated a strong association between TE treatment strategy and improvement in visual acuity at 12 months.

Conclusion: Eyes treated according to TE had better visual outcome at 12 months. The results indicate that treatment according to proactive TE-regimen is superior to treatment according to PRN-regimen in clinical routine care of nAMD.

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Other treatments

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Recombinant manganese peroxidase reduces A2E burden in age related and Stargardt's macular degeneration models.

Moody KJ, Tinklepaugh J, Obert E, et al.

Abstract: Macular degeneration is hallmarked by retinal accumulation of toxic retinoid species (e.g. A2E) for which there is no endogenous mechanism to eliminate. This ultimately results in progressive dysfunction and loss of vision either in advanced age for genetically normal patients (age-related macular degeneration), or in adolescence for those with inherited genetic mutations (Stargardt's disease). Here, we present a proof-of-concept study for an enzyme-based therapy to remove these retinoids, modeled on traditional enzyme replacement therapy. Recombinant manganese peroxidase (rMnP) is produced in Pichia pastoris. In vitro, we demonstrate that rMnP breaks down A2E and other lipofuscin fluorophores with limited cellular toxicity, and as this enzyme is mannosylated, it can be taken up into cells via mannose receptor-dependent endocytosis. In vivo we demonstrate that rMnP can significantly reduce the A2E burden when administered by intravitreal injections. Together, these data provide encouraging results towards the development of an enzyme-based therapy for macular degeneration and indicate the need for additional work to characterize the molecular mechanism of A2E breakdown and to improve the pharmacological parameters of the enzyme.

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Diagnosis


Lages V, Gehrig B, Herborot CP Jr.

Background: Intravitreal injection of anti-vascular endothelial growth factor agents is the most common intraocular procedure worldwide, inevitably causing more cases of post-injection endophthalmitis. The purpose of this study was to evaluate the utility of laser flare photometry in monitoring inflammation after intravitreal injection of anti-vascular endothelial growth factor agents, particularly to detect early stage post-injection endophthalmitis. A retrospective case review was performed of all patients who underwent flare assessment by laser flare photometry before and after intravitreal injection of bevacizumab or aflibercept at the Centre for Ophthalmic Specialized Care in Lausanne, Switzerland, between January 2015 and May 2018. The following data were retrieved: indication for intravitreal injection, medication administered, pre-injection and 72-h post-injection laser flare photometry values, and occurrence of post-injection endophthalmitis. A total of 736 injections were included in this study; 705 cases (95.8%) had a post-
injection flare at 72 h ≤ 30 ph/ms, 29 cases (3.9%) had a post-injection flare at 72 h between > 30 and 50 ph/ms, and 2 cases (0.3%) had a post-injection flare at 72 h above > 50 ph/ms (664 and 742 ph/ms). These latter two cases were diagnosed as early-stage endophthalmitis.

**Conclusion**: Laser flare photometry is a cost-effective method of screening for early stage post-injection endophthalmitis. Values > 50 ph/ms 72-h post-injection should prompt immediate evaluation by an ophthalmologist.

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**Macular vessel reduction as predictor for recurrence of macular oedema requiring repeat intravitreal ranibizumab injection in eyes with branch retinal vein occlusion.**

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**Aim**: To determine whether there are factors that can predict the frequency of recurrences of macular oedema associated with branch retinal vein occlusion (BRVO).

**Methods**: We reviewed the medical records of 31 eyes with treatment-naïve macular oedema associated with BRVO. All eyes received an intravitreal ranibizumab (IVR) injection and were followed with a pro re nata protocol for at least 12 months. A reinjection of ranibizumab was performed when the central foveal thickness was ≥300 µm. At 1 month after IVR injection, the macular vessel reduction was calculated by comparing the vessel density in the optical coherence tomography angiography in the BRVO involved half to that in the non-involved half.

**Results**: The mean visual acuity improved from 0.35±0.27 logarithm of the minimal angle of resolution (logMAR) units (20/45; Snellen) at initial visit to 0.06±0.15 logMAR units (20/23) at 12 months (p<0.0001). During 12 months, the mean number of IVR injections was 3.8±1.8. Multivariate regression analysis showed that a greater macular vessel reduction at 1 month after initial IVR injection was significantly a negative predictor of frequency of IVR injections (β=-0.5065, p = 0.0082). The visual acuity and the central foveal thickness at the initial visit or at 1 month after initial IVR injection were not predictive factors for frequency of IVR injections.

**Conclusions**: Patients with BRVO with a large macular vessel reduction at 1 month after an initial IVR injection have fewer recurrences and thus lower frequency of IVR injections during 12 months.

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**Atrophy in neovascular age-related macular degeneration: Age-Related Eye Disease Study 2 Report Number 15.**


**Purpose**: To identify the development and progression of macular retinal pigment epithelial atrophy in eyes with neovascular (CNV) age-related macular degeneration (AMD) and to correlate with visual acuity (VA).

**Design**: Cohort study.

**Participants**: Age-Related Eye Disease Study 2 (AREDS2) participants with intermediate AMD enrolled in a randomized controlled clinical trial of oral supplements. Analyses were conducted in the subset of AREDS2 participants who were also enrolled in the fundus autofluorescence ancillary (FAF) ancillary study.

**Methods**: Color photographs and FAF images were evaluated in eyes that developed CNV. Presence of geographic atrophy (GA) prior to the incidence of CNV and the development of macular atrophy following incident CNV were assessed. Areas of hypofluorescence representing atrophy were measured for area
and macular involvement. Enlargement rate of atrophy and change in visual acuity over time were analyzed.

**Main Outcome Measures:** Incidence and enlargement rate of atrophy and VA changes in eyes with incident CNV.

**Results:** Incident CNV developed in 334 (9.2%) of eyes evaluated in the AREDS2 FAF substudy. Of these, 40% had macular atrophy at incidence of CNV with half of these attributable to pre-existing GA. Atrophy developed in 14.7% of eyes over 4 years of follow-up. Mean area of atrophy was largest in eyes with pre-existing GA and CNV (5.17 mm², p<0.001), and atrophy involved the center of the macula in > 65% of eyes. Mean VA letter score at the annual visit in which CNV was documented was similar in the three groups with atrophy; eyes with CNV and pre-existing GA, incident atrophy at the first visit with CNV, and atrophy during follow up (60 letters). Enlargement rate of atrophy was also similar in eyes in the three groups (1.23 - 1.86 mm², p = 0.47). Eyes with macular atrophy lost more visual acuity compared to eyes without atrophy, particularly after 2 years of follow-up (-10.9 vs. -3.6 letters, p = 0.07).

**Conclusion:** Atrophy is commonly seen in neovascular AMD and often can be attributed to pre-existing GA. Macular atrophy and GA appear to be a continuum of the same disease process and are both associated with poor vision.


**Pathogenesis**


**Oxidative stress damage circumscribed to the central temporal retinal pigment epithelium in early experimental non-exudative age-related macular degeneration.**


**Abstract:** Non-exudative age-related macular degeneration (NE-AMD) represents the leading cause of blindness in the elderly. The macular retinal pigment epithelium (RPE) lies in a high oxidative environment because its high metabolic demand, mitochondria concentration, reactive oxygen species levels, and macular blood flow. It has been suggested that oxidative stress-induced damage to the RPE plays a key role in NE-AMD pathogenesis. The fact that the disease limits to the macular region raises the question as to why this area is particularly susceptible. We have developed a NE-AMD model induced by superior cervical ganglionectomy (SCGx) in C57BL/6J mice, which reproduces the disease hallmarks exclusively circumscribed to the temporal region of the RPE/outer retina. The aim of this work was analyzing RPE regional differences that could explain AMD localized susceptibility. Lower melanin content, thicker basal infoldings, higher mitochondrial mass, and higher levels of antioxidant enzymes, were found in the temporal RPE compared with the nasal region. Moreover, SCGx induced a decrease in the antioxidant system, and in mitochondria mass, as well as an increase in mitochondria superoxide, lipid peroxidation products, nuclear Nrf2 and heme oxygenase-1 levels, and in the occurrence of damaged mitochondria exclusively at the temporal RPE. These findings suggest that despite the well-known differences between the human and mouse retina, it might not be NE-AMD pathophysiology which conditions the localization of the disease, but the macular RPE histologic and metabolic specific attributes that make it more susceptible to choroid alterations leading initially to a localized RPE dysfunction/damage, and secondarily to macular degeneration.

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**Wnt Signaling in vascular eye diseases.**

Wang Z, Liu CH, Huang S, Chen J.
Abstract: The Wnt signaling pathway plays a pivotal role in vascular morphogenesis in various organs including the eye. Wnt ligands and receptors are key regulators of ocular angiogenesis both during the eye development and in vascular eye diseases. Wnt signaling participates in regulating multiple vascular beds in the eye including regression of the hyaloid vessels, and development of structured layers of vasculature in the retina. Loss-of-function mutations in Wnt signaling components cause rare genetic eye diseases in humans such as Norrie disease (ND), and familial exudative vitreoretinopathy (FEVR) with defective ocular vasculature. On the other hand, experimental studies in the more prevalent vascular eye diseases, such as wet age-related macular degeneration (AMD), diabetic retinopathy (DR), retinopathy of prematurity (ROP), and corneal neovascularization, suggest that aberrantly increased Wnt signaling is one of the causations for pathological ocular neovascularization, indicating the potential of modulating Wnt signaling to ameliorate pathological angiogenesis in eye diseases. This review recapitulates the key roles of the Wnt signaling pathway during ocular vascular development and in vascular eye diseases, and pharmaceutical approaches targeting the Wnt signaling as potential treatment options.

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Case Reports


Macular pigment density changes in central serous chorioretinopathy.

Aim: To present a series of 2 cases of central serous chorioretinopathy and the changes in the macular pigment optical density during the evolution of the disease.

Material and methods: A 32-year-old patient presented himself for blurred vision on his LE. The SD OCT imaging revealed serous macular detachment of the neurosensory retina on the LE. The MPOD results were 0.72 on RE and 0.91 on LE. After treatment and resorption of the subretinal fluid, the MPOD values were 0.72 on the RE and 0.82 on the LE. The second patient was a 36-year-old male with metamorphopsia on LE and serous macular detachment on this eye. The MPOD results were 0.43 on RE and 0.58 on the LE and, after treatment, they were 0.38 on the RE and 0.43 on the LE.

Conclusions: Central serous chorioretinopathy is a disease of unknown pathophysiology in which we observed a higher MPOD on the eye with CSC than on the fellow eye and a decrease in the MPOD value after the resorption of the subretinal fluid. Abbreviations: L = lutein, Z = zeaxantin, MZ = mezozeaxantin, AMD = age related macular degeneration, MPOD = macular pigment optical density, MP = macular pigment, HFP = Heterochromatic Flicker Photometry, CSC = central serous chorioretinopathy, RE = right eye, LE = left eye.

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Lamellar macular hole formation following intravitreal bevacizumab injection for choroidal neovascularization by age-related macular degeneration.
Torabi H, Jadidi K, Naderi M.

Abstract: This report describes a lamellar macular hole formation subsequent to intravitreal bevacizumab injection for the treatment of choroidal neovascularization (CNV) by age-related macular degeneration. A 67-year-old woman with bilateral CNV underwent 3 monthly intravitreal bevacizumab injections in her both eyes. One month after the third bilateral injection, vision loss happened. Optical coherence tomography performed for further evaluation that showed reduction of intra- and sub-retinal fluid associated with lamellar macular detachment in both eyes. Although macular hole formation, especially bilateral form, is a rare complication of intravitreal injections, surgeons should consider macular hole development in cases with vision deterioration following intravitreal bevacizumab injection.