

## BIOMARKERS

### OCT-Based Biomarkers are Associated with Systemic Inflammation in Patients with Treatment-Naïve Diabetic Macular Edema.

Ophthalmology & Therapy 2022 Sep 27

Zhou J, Song S, Zhang Y, Jin K, Ye J.

**Introduction:** Diabetic macular edema (DME) is one of the major sight-threatening complications of diabetic retinopathy, which is associated with retinal inflammation. However, it is still unknown whether DME is associated with systemic inflammation. The study aimed to investigate the association between systemic inflammatory and optical coherence tomography (OCT) biomarkers in patients with treatment-naïve center-involving diabetic macular edema (DME) and to further explore the role of systemic inflammation in DME.

**Methods:** Medical records including clinical characteristics and ophthalmic examinations were collected from patients with treatment-naïve center-involving DME. Systemic inflammation markers including systemic immune-inflammatory index (SII), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) were calculated. OCT biomarkers, including intraretinal cyst (IRC) size, disorganization of retinal inner layers (DRIL), external limiting membrane (ELM)/ellipsoid zone (EZ) integrity, retinal hyperreflective foci (HRF), subretinal fluid (SRF) and vitreomacular (VM) status were evaluated manually. Correlation analysis and multivariable linear regression models were used to investigate the relationship between systemic inflammatory markers and OCT biomarkers.

**Results:** A total of 82 patients with treatment-naïve center-involving DME were included. The number of HRF on OCT was correlated with SII, NLR, and PLR and positively associated with SII ( $p < 0.001$ ) in both univariate and multivariate linear regression analyses. The differences remained largely the same during subgroup analysis controlling DM duration, SRF, and ELM/EZ integrity. No significant association was observed between other OCT biomarkers and blood inflammatory markers.

**Conclusion:** Retinal HRF in diabetic macular edema is associated with blood inflammatory markers, which supports the theory of HRF's inflammatory nature and emphasizes the important role of inflammation in DME. SII may be a potential marker for DME treatment decisions.

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## DRUG TREATMENT

### Associations with visual acuity outcomes after 12 months of treatment in 9401 eyes with neovascular AMD.

BMJ Open Ophthalmology. 2022 Jun

Relton SD, Chi GC, Lotery A, West RM; Real world AMD treatment outcomes EMR User Group, McKibbin M.

**Objective:** To record visual acuity outcomes after 12 months of treatment for neovascular age-related macular degeneration (NvAMD), investigate variation between sites and explore associations with baseline characteristics and care processes.

**Methods and Analysis:** Anonymised demographic and clinical data were extracted from electronic medical records at treating National Health Service (NHS) Trusts. Associations with acuity outcomes were investigated using multivariate linear and logistic regression.

**Results:** Analysis included 9401 eyes (7686 patients) treated at 13 NHS Trusts. From baseline to month 12, median acuity improved from LogMAR 0.50 (IQR 0.30-0.80) to 0.40 (0.22-0.74) and the proportion of eyes with LogMAR  $\geq 0.3$  increased from 34.5% to 39.8%. Baseline visual acuity was the strongest predictor of visual acuity outcomes. For each LogMAR 0.1 worsening of baseline acuity, the acuity at 12 months was improved by LogMAR 0.074 (95% CI 0.073 to 0.074) and the odds of a 'poor' acuity outcome was multiplied by 1.66 (95% CI 1.61 to 1.70). Younger age, independent living status, lower socioeconomic deprivation, timely loading phase completion and higher number of injections were associated with better acuity outcomes. Despite case-mix adjustments, there was evidence of significant variation in acuity outcomes between sites.

**Conclusions:** Even after adjustment for other variables, variation in acuity outcomes after NvAMD treatment within the NHS remains. Meaningful comparison of outcomes between different providers requires adjustment for a range of baseline characteristics, not visual acuity alone. Identifying best practice at sites with better outcomes and adapting local care processes are required to tackle this health inequality.

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## **Hemodynamic Effects of Anti-Vascular Endothelial Growth Factor Injections on Optical Coherence Tomography Angiography in Diabetic Macular Edema Eyes.**

Translational Vision Science & Technology 2022 Oct 3

Song J, Huang BB, Ong JX, Konopek N, Fawzi AA.

**Purpose:** To evaluate retinal hemodynamic responses to anti-vascular endothelial growth factor (VEGF) injection in eyes with diabetic macular edema using optical coherence tomography angiography (OCTA). We performed a comparison of two different thresholding methods to identify the most accurate for studying the vessel density (VD) in diabetic macular edema eyes.

**Methods:** The study prospectively included 26 eyes of 22 subjects (aged  $60.2 \pm 13.7$  years) who underwent OCTA scan before and after anti-VEGF injection (mean interval between OCTA =  $31.1 \pm 17.3$  days). We analyzed adjusted flow index, VD, and Skeletonized vessel length density in the parafoveal area (3-mm annulus with a 1-mm inner circle), along with full-thickness fovea avascular zone area and central foveal thickness (CFT). Using averaged scans VD as the ground truth, we compared two different algorithms for VD at the different plexuses. Longitudinal changes were assessed using a generalized linear model correcting for central foveal thickness and Q-score.

**Results:** We found significantly decreased adjusted flow index in the DCP layer ( $P = 0.010$ ) at the follow-up. Furthermore, foveal avascular zone ( $P < 0.001$ ) and central foveal thickness ( $P = 0.003$ ) showed significant decrease on follow-up compared with baseline. Comparing the thresholding algorithms showed that vessel length density-based thresholding was more accurate for quantifying the DCP VD.

**Conclusions:** The adjusted flow index decreased significantly in the DCP layer on follow-up OCTA scan, suggesting vascular flow disruption and decreased deep retinal perfusion after anti-VEGF

injection. Our results also highlight the fact that the choice of thresholding method is particularly critical for DCP quantification in eyes with diabetic macular edema.

**Translational Relevance:** Findings confirmed impaired deep retinal capillary flow after anti-VEGF injection.

DOI: [10.1167/tvst.11.10.5](https://doi.org/10.1167/tvst.11.10.5)

### **Differences in clinical characteristics and treatment outcomes of submacular hemorrhage caused by age-related macular degeneration and retinal macroaneurysms: A multicenter survey from the Japan Clinical Retina Study (J-CREST) group.**

PLoS One. 2022 Sep 29

Kimura T, Araki T, Yasukawa T, Kato A, Kuwayama S, Kinoshita T, Okamoto F, Murakami T, Mitamura Y, Sakamoto T, Terasaki H, Kusuhara S, Miki A, Takamura Y, Kondo M, Matsubara H, Ueda T, Tsujinaka H, Gomi F.

**Purpose:** To evaluate the clinical characteristics, treatment trends, and visual prognosis of submacular hemorrhage (SMH) secondary to neovascular age-related macular degeneration (nAMD) and retinal arterial macroaneurysm (RAM).

**Methods:** This retrospective study enrolled 187 Japanese patients with SMH at 10 institutions from 2015 to 2018. Medical records including SMH etiology, best-corrected visual acuity (BCVA), fundus photographs, optical coherence tomography images, and selected treatments were analyzed.

**Results:** Major causes of SMH were typical nAMD (tnAMD) (18%), polypoidal choroidal vasculopathy (PCV) (50%) and RAM (29%). Age, male/female ratio, baseline BCVA, central retinal thickness, and involved retinal layers were significantly different between etiologies (all  $P < 0.0001$ ). Treatment with anti-vascular endothelial growth factor drugs with and without intravitreal gas injection was chosen for half of eyes in the tnAMD and PCV groups, whereas vitrectomy was performed in 83.7% of eyes with RAM. The final BCVA improved significantly from baseline in the PCV and RAM groups ( $P = 0.0009$ ,  $P < 0.0001$ ) and final BCVA was significantly better in the PCV group at a level similar to the other groups ( $P = 0.0007$ ,  $P = 0.0008$ ). BCVA improvement from baseline was significantly greater in the RAM group compared with the tnAMD ( $P = 0.0152$ ) and PCV ( $P = 0.017$ ) groups. Multivariate analysis revealed better final BCVA was significantly associated with younger age ( $P = 0.0054$ ), better baseline BCVA ( $P = 0.0021$ ), RAM subtype ( $P = 0.0446$ ), and no tnAMD ( $P = 0.001$ ).

**Conclusions:** The characteristics of, and treatment strategy for, SMH were different between the underlying diseases. Anti-vascular endothelial growth factor treatment with or without expansile gas was mainly chosen for SMH in tnAMD and PCV, whereas vitrectomy with gas was the most common treatment for RAM, and the higher rate for vitrectomy might result in the greater BCVA improvement in the RAM group than in the other groups. Final BCVA was better in PCV, RAM, and tnAMD, in that order, because patients with PCV were younger and had better baseline BCVA.

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### **Characteristics of age-related macular degeneration showing a poor response to three loading doses of anti-VEGF.**

Retina. 2022 Sep 23

Song YY, Jun JH, Kim JT, Lee SC, Lee MW.

**Purpose:** To analyze the clinical features of refractory age-related macular degeneration (AMD) patients associated with the response to three consecutive loading doses of anti-vascular endothelial growth factor (VEGF).

**Methods:** A retrospective chart review was performed on typical exudative AMD patients treated by three consecutive anti-VEGF injections. The patients were divided into a group without residual fluid on optical coherence tomography (OCT) images (Group 1) and a group with residual fluid (Group 2). We analyzed qualitative and quantitative morphological features of OCT and OCT angiography (OCTA). We performed univariate and multivariate logistic regression analyses to identify factors associated with the treatment response.

**Results:** We enrolled a total of 90 patients (Group 1: n = 60 , Group 2: n = 30). Under OCT, the choroidal thickness (CT) differed significantly between groups 1 and 2 ( $246.60 \pm 67.67$  vs.  $286.90 \pm 40.92$   $\mu\text{m}$ ,  $p = 0.001$ ). Under OCTA, The presence of branching (48.3% vs. 73.3%,  $p = 0.024$ ), loops (31.7% vs. 66.7%,  $p = 0.002$ ) and a peripheral arcade (40.0% vs. 76.7%,  $p = 0.001$ ) differed significantly. Logistic regression analysis showed that the initial CT ( $B = 0.012$ ;  $p = 0.007$ ), presence of loops ( $B = 1.289$ ;  $p = 0.015$ ) and peripheral arcade ( $B = 1.483$ ;  $p = 0.008$ ) significantly affected the anti-VEGF treatment response.

**Conclusions:** A thicker choroid and the presence of loops and a peripheral arcade were significantly associated with a poorer response to three loading anti-VEGF injections in typical exudative AMD patients.

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## OTHER TREATMENTS

### Do patients with unilateral macular neovascularization type 3 need AREDS supplements to slow the progression to advanced age-related macular degeneration?

Eye (London). 2022 Sep 29

Haj Najeeb B, Schmidt-Erfurth U.

Given the wide spectrum of unique characteristics of macular neovascularization type 3 (MNV3) compared with types 1 and 2, we suggest regrading the colour photography assessment of the AREDS study to verify the impact of AREDS supplements on eyes with MNV3.

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## CASE REPORTS

### Posterior scleritis after biweekly aflibercept intravitreal injections.

American Journal of Ophthalmology Case Reports 2022 Sep 6

Hébert M, You E, Gravel JF, Dirani A, Bourgault S.

**Purpose:** To describe a case of posterior scleritis following anti-vascular endothelial growth factor (VEGF) injection.

**Observations:** A 51-year-old male receiving biweekly anti-VEGF injections for a central retinal vein occlusion complicated with cystoid macular edema presented with new-onset severe pain, photophobia, and tearing. Ophthalmological examination revealed choroidal folds and B-scan ultrasound confirmed significant thickening of the sclera, leading to a diagnosis of posterior scleritis. This resolved under topical and systemic corticosteroids.

**Conclusions and importance:** Intravitreal anti-VEGF injections could be associated with non-infectious posterior scleritis. Clinicians should be particularly aware of this possibility in patients receiving frequent injections.

DOI: [10.1016/j.ajoc.2022.101696](https://doi.org/10.1016/j.ajoc.2022.101696)

## REVIEWS

### Review of fibrosis in neovascular age-related macular degeneration.

American Journal of Ophthalmology. 2022 Sep 23

Cheong KX, Cheung CMG, Teo KYC.

**Purpose:** To report the diagnosis and definitions, epidemiology, risk factors, and visual outcomes of fibrosis in neovascular age-related macular degeneration (nAMD)

**Design:** Systematic review and meta-analysis **METHODS:** The review was performed using the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Observational studies and randomised controlled trials were included.

**Results:** The identification of fibrosis is challenging. Optical coherence tomography angiography and polarisation-sensitive optical coherence tomography represent novel options in multimodal imaging. The prevalence of fibrosis at baseline, 12, 24, and 60 months are 13%, 32%, 36%, and 56%, respectively. Approximately 60% of the fibrosis burden in nAMD at five years is present in the first year of treatment. Fibrosis development is the highest in the first 12 months and slows down over time. The risk factors of fibrosis include classic choroidal neovascularisation (CNV), intra-retinal fluid, haemorrhage, hyperreflective material, CNV lesion size, and retinal thickness. Sub-retinal fluid and pigment epithelial detachment may be protective. Treatment-associated factors include disease activity and time to diagnosis. At baseline, the best corrected visual acuity in eyes with fibrosis is poorer than in eyes without fibrosis (-18.50 letters). This difference became larger at 12 months despite treatment (-26.86 letters).

**Conclusions:** There is a need to identify effective treatment strategies for fibrosis, and to monitor at-risk patients closely. More studies involving multimodal imaging are required to clarify the definitions and grading criteria for fibrosis.

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## EARLY RESEARCH

**Long-term observations of macular thickness after subretinal implantation of a photovoltaic prosthesis in patients with atrophic age-related macular degeneration.**

**Objective:** Subretinal prostheses electrically stimulate the residual inner retinal neurons to partially restore vision. We investigated the changes in neurosensory macular structures and its thickness associated with subretinal implantation in geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

**Approach:** Using optical coherence tomography, changes in distance between electrodes and retinal inner nuclear layer as well as alterations in thickness of retinal layers were measured over time above and near the subretinal chip implanted within the atrophic area. Retinal thickness was quantified across the implant surface and edges as well as outside the implant zone to compare with the natural macular changes following subretinal surgery, and the natural course of dry AMD.

**Main Results:** GA was defined based on complete retinal pigment epithelium and outer retinal atrophy (cRORA). Based on the analysis of 3 patients with subretinal implantation, we found that the distance between the implant and the target cells was stable over the long-term follow-up. Total retinal thickness above the implant decreased on average, by  $39 \pm 12 \mu\text{m}$  during 3 months post-implantation, but no significant changes were observed after that, up to 36 months of the follow-up. Retinal thickness also changed near the temporal entry point areas outside the implantation zone following the surgical trauma of retinal detachment. There was no change in the macula cRORA nasal to the implanted zone, where there was no surgical trauma or manipulation.

**Significance:** The surgical delivery of the photovoltaic subretinal implant causes minor retinal thickness changes that settle after 3 months, and then remain stable over long-term with no adverse structural or functional effects. Distance between the implant and the inner nuclear layer remains stable up to 36 months of the follow-up.

DOI: [10.1088/1741-2552/ac9645](https://doi.org/10.1088/1741-2552/ac9645)