Drug treatment


Functional characterization of abicipar-pegol, an Anti-VEGF DARPin therapeutic that potently inhibits angiogenesis and vascular permeability.


**Purpose:** DARPin molecules are a novel class of small proteins that contain engineered ankyrin repeat domain(s) and bind to target proteins with high specificity and affinity. Abicipar-pegol (abicipar), a DARPin molecule targeting vascular endothelial growth factor-A (VEGF-A), is currently under evaluation in patients with age-related macular degeneration. The pharmacodynamic properties of abicipar were characterized using in vivo and in vitro assays.

**Methods:** The binding affinity of abicipar was assessed using a kinetic exclusion assay (KinExA). In vitro assays evaluated abicipar effects on VEGF-A165-induced calcium mobilization and tube formation in human umbilical vein endothelial cells. Abicipar was tested in vivo in a mouse model of corneal neovascularization and a rabbit model of chronic retinal neovascularization. The efficacies of abicipar and ranibizumab were compared in a rabbit model of VEGF-A165-induced retinal vasculopathy.

**Results:** Abicipar has a high affinity for the soluble isoforms of VEGF-A; binding affinities for human VEGF-A165 are approximately 100-fold greater than those of ranibizumab and bevacizumab and are similar for rat VEGF-A164 but approximately 20-fold lower for rabbit VEGF-A165. Abicipar was effective in cell-based and in vivo models of angiogenesis and vascular leak, blocking neovascularization in a mouse model of corneal neovascularization and vascular permeability in a rabbit model of chronic neovascularization. In a rabbit model of VEGF-A165-induced vasculopathy, the duration of effect of abicipar was longer than ranibizumab when the two compounds were administered at molar-equivalent doses.

**Conclusions:** These data support the testing of abicipar as a treatment for retinal diseases characterized by neovascularization and vascular leak.

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Effects of smoking on outcomes of antivascular endothelial growth factor therapy in patients with neovascular age-related macular degeneration: smoking and anti-VEGF therapy in nAMD.


Purpose: To evaluate the effect of smoking on the outcome of antivascular endothelial growth factor (VEGF) therapy in patients with neovascular age-related macular degeneration (nAMD).

Methods: This retrospective case-control study included 64 eyes in 59 patients with treatment-naive nAMD. Smoking habits were obtained from hospital records and patient recall. The patients were divided into ever-smokers and never-smokers. The patients were treated with ranibizumab or aflibercept for at least 1 year. Outcome measures were best-corrected visual acuity (BCVA), central retinal thickness (CRT) at the fovea, subfoveal choroidal thickness (SCT), and number of injections received.

Results: There were no statistically significant differences in BCVA, CRT, or SCT changes between ever-smokers and never-smokers. The number of injections received was significantly higher in ever-smokers with a history of heavy smokers (never-smokers vs. heavy smokers: 5.3 ± 2.6/year vs. 7.3 ± 2.5/year; P=0.048 and mild smokers vs. heavy smokers: 5.2 ± 2.5/year vs. 7.3 ± 2.5/year; P=0.043). There was no significant difference in the baseline CRT or presence of atrophic retinal pigment epithelium in the fellow eyes of patients with nAMD according to smoking status; however, the baseline CRT in eyes with nAMD was significantly thinner in ever-smokers than in never-smokers (P=0.02).

Conclusion: The anti-VEGF therapy was frequently required in nAMD patients with a history of heavy smoking. Heavy smoking could cause poor therapeutic response in nAMD patients.

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Characterisation of poor visual outcomes of neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor agents.


Purpose: To investigate the incidence, characteristics and baseline predictors of poor visual outcomes in eyes with neovascular age-related macular degeneration (nAMD) receiving intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents in daily clinical practice.

Design: Observational study.

Participants: Treatment-naive eyes starting anti-VEGF therapy for nAMD between 2007 and 2012 tracked in the Fight Retinal Blindness! registry. Cases had sustained ≥15 letters of loss from baseline without recovery of visual acuity (VA) at final endpoint. A subgroup analysis included eyes that sustained ≥30 letters of loss. Controls had not sustained ≥15 letters of loss.


Main Outcome Measures: The proportion of eyes with sustained VA loss within 5 years, the time to development of sustained VA loss and baseline predictors of sustained VA loss.

Results: There were 1760 eyes in total and 856 eyes that completed 5 years follow-up. The proportion of eyes with sustained VA loss of ≥15 letters at 5 years was 22.9% (95%CI, 20.7-25.1) and VA loss of ≥30 letters was 10.8% (95%CI, 9.1-12.5). Factors independently associated with higher incidence of sustained ≥15 letter loss included age >80 years (odds ratio [OR], 1.33 for patients >80 years vs. ≤80 years; 95%CI, 1.05-1.69; P=.02), fewer injections (OR, 0.97 per injection; 95%CI, 0.96-0.98; P=.0005) and more visits at which the choroidal neovascularisation was graded as active (OR, 1.97 for eyes in upper quartile of active visits vs. eyes in lowest quartile of active visits; 95%CI, 1.39-2.79; P=.0001). Baseline VA≥70 letters was
associated with reduced risk of sustained ≥30 letter loss (OR, 0.61; 95%CI, 0.38-0.98; P=.04). Baseline angiographic lesion criteria were not significantly associated with sustained VA loss.

Conclusions: Twenty-three percent of eyes with nAMD developed sustained VA loss of ≥15 letters over 5 years of anti-VEGF therapy. Baseline predictors of poor outcomes provide more accurate assessment of the potential benefit from anti-VEGF therapy.

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Sequence effect in the treatment of proliferative diabetic retinopathy with intravitreal ranibizumab and panretinal photocoagulation.


Purpose: To compare the outcome of the sequence in the two treatments (intravitreal ranibizumab and panretinal photocoagulation) in high-risk proliferative diabetic retinopathy.

Methods: This retrospective study included 35 patients with newly diagnosed high-risk proliferative diabetic retinopathy in 43 eyes; 18 (22 eyes) received intravitreal ranibizumab before panretinal photocoagulation (intravitreal ranibizumab+ group), while the other 17 (21 eyes) received panretinal photocoagulation before intravitreal ranibizumab (panretinal photocoagulation+ group). Each subject received three intravitreal ranibizumabs that were interleaved with three panretinal photocoagulations. The first treatment (either intravitreal ranibizumab or panretinal photocoagulation) was done 1 week before the second one. The interval between intravitreal ranibizumabs was 4 weeks, panretinal photocoagulation was 2 weeks. The power and pulse duration were determined based upon the status of each retinal spot before each panretinal photocoagulation. The retinal non-perfusion region was measured with fundus fluorescein angiography before and 1 month after the final treatment. The central macular thickness was measured with optical coherence tomography within 1 week before the first treatment, before each panretinal photocoagulation, and 1 month after the final intravitreal ranibizumab.

Results: The panretinal photocoagulation energy required for effective treatment was lower in intravitreal ranibizumab+ group in the first and second sessions and in total energy (p < 0.05). Central macular thickness reduction before the second panretinal photocoagulation session was significant in the intravitreal ranibizumab+ group (p < 0.05).

Conclusion: The sequence used in intravitreal ranibizumab+ group showed clear advantages over that in panretinal photocoagulation+ group in the treatment of proliferative diabetic retinopathy, not only in the use of lower energy for panretinal photocoagulation but also in the more rapid regression of neovascularization and less need of additional treatment.

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Vascular remodeling of choroidal neovascularization in older myopic patients treated with ranibizumab.


Purpose: To investigate morphological changes in myopic choroidal neovascularization (mCNV) using optical coherence tomography-angiography (OCT-A) after treatment with ranibizumab.

Methods: Retrospective analysis of consecutive patients over a 24-month period. All treatment-naïve mCNV were imaged at baseline with color pictures, spectral-domain OCT and OCT-A, and fluorescein angiography in selected cases. CNV morphology was classified at baseline and at 6 months. The CNV lesion surface was also compared.

Results: Twenty-nine patients with a mean age of 70.3 ± 10.1 years were included. They received a mean
number of 2.65 injections over 6 months. Best-corrected visual acuity improved from 62.2 to 68.5 letters (p = 0.004), with regression of exudation in 24 eyes (82.7%). Baseline CNV was classified into tree-in-bud (16 eyes), medusa (9 eyes), or sea-fan (4 eyes) pattern. At 6 months, no abnormal blood flow was observed in CNV in 13 eyes. Eyes with complete regression or evolution towards an indistinct pattern showed more often a complete regression of exudation than eyes with unchanged pattern (p = 0.007). The mean CNV surface significantly decreased from 0.19 to 0.08 mm² (p < 0.0001).

**Conclusion:** An unchanged pattern was more often associated with exudation persistence, while a complete regression or evolution towards indistinct pattern was always associated with vascular inactivity. However, variable changes in mCNV were observed after anti-VEGF. Thus, OCT-A could be more useful in the diagnosis than in the follow-up of mCNV.

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**Retinal metabolic and structural alterations in response to aflibercept treatment in neovascular age-related macular degeneration.**

Jakobsen DB, Torp TL, Stefansson E, et al.

**Purpose:** Non-invasive retinal markers of disease activity could pave the way for individualized treatment in neovascular age-related macular degeneration (nAMD). We aimed to evaluate if retinal vascular oxygen saturation and calibres could predict the initial treatment response after a loading phase of intravitreal aflibercept in nAMD.

**Method:** A total of 149 eyes were included (nAMD, n = 76; dry AMD, n = 30; normal eyes n = 43). Of these, 57 treatment-naïve eyes with nAMD received three monthly injections with 2.0 mg aflibercept and were subsequently stratified according to functional and structural response according to development in best-corrected visual acuity and macular retinal thickness. The retinal vascular oxygen saturation and calibres were measured prior to treatment and 1 month after the third injection.

**Results:** Patients with nAMD and dry AMD had higher retinal arteriolar oxygen saturation as compared to normal eyes (94.3% versus 95.2% versus 92.6%, p = 0.04). Thirty-nine (68.4%) and 12 (21.1%) eyes with nAMD were functional and structural responders. After the loading phase, structural nonresponders developed a higher retinal arteriolar (95.3% versus 93.3%, p = 0.03) and venular (64.7% versus 59.4%, p = 0.02) oxygen saturation, and responders developed a lower retinal arteriolar calibre (118.0 versus 114.3 μm, p < 0.01). In a multiple logistic regression model, increasing retinal venular oxygen saturation associated with a negative structural treatment outcome (odds ratio 1.17 for each 1% increment after the loading phase, 95% confidence interval 1.01-1.36, p = 0.03).

**Conclusion:** Changes in the retinal venular oxygen saturation associate independently with initial treatment response in nAMD, but functional and structural retinal measurements prior to treatment could not predict the treatment response.

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**Dynamics of soluble vascular endothelial growth factor receptors and their ligands in aqueous humour during ranibizumab for age-related macular degeneration.**


**Background:** Intravitreal ranibizumab injection (IRI) is effective for patients with exudative age-related macular degeneration (AMD) and decreases intraocular levels of vascular endothelial growth factor (VEGF), but VEGF receptor intraocular dynamics after IRI are unclear. Therefore, we evaluated changes in the aqueous humor levels of soluble vascular endothelial growth factor receptor (sVEGFR)-1, sVEGFR-2, and their ligands for these receptors (VEGF) patients with AMD receiving IRI.
Methods: The subjects were 24 patients with AMD (24 eyes) who received 3 doses of IRI at monthly intervals. Aqueous humor samples were obtained when each IRI dose was given (visits 0, 1, and 2 at 4-week intervals). Then the suspension array method was employed to measure sVEGFR-1, sVEGFR-2, VEGF, and placental growth factor (PIGF) in aqueous humor samples from the 24 AMD patients and 13 cataract patients (as controls). Best corrected visual acuity (BCVA; logMAR) chart and central macular thickness (CMT; optical coherence tomography) were also assessed over time.

Results: At baseline, the aqueous humor levels of sVEGFR-1, sVEGFR-2, VEGF, and PIGF were significantly higher in the AMD group than in the control group. There was a significant correlation between VEGF and PIGF or between sVEGFR-1 and sVEGFR-2. BCVA and CMT both improved significantly after IRI, and the aqueous humor levels of VEGF, PIGF, and sVEGFR-1 also decreased significantly.

Conclusions: VEGFRs may be involved in the pathogenesis of AMD. IRI improves clinical parameters in AMD patients by suppressing intraocular levels of VEGF, PIGF, and sVEGFR-1.

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Other treatments

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Curcumin: A new candidate for retinal disease therapy?
Farajipour H, Rahimian S, Taghizadeh M.

Abstract: The retina is the neural portion and light-sensitive layer of the eye, which has been observed in most of the vertebrates. The retina is composed of light-sensitive cells that absorb light and convert it into neural signals. These signals are sent to the brain for visual recognition. It has been shown that many pathogenesis conditions, including inflammation, angiogenesis, oxidative stress, and imbalanced histone modifications in the retina are associated with initiation and progression of retinal diseases (ie, glaucoma, diabetic retinopathy, and age-related macular degeneration). Currently available treatments include laser surgery, freezing, stem-cell therapy, shrinking abnormal blood vessels. It has some limitations, such as invasive methods, high costs, and many side effects. Hence, finding a new therapeutic platform for stopping or slowing of the disease progression is required. Curcumin is a natural product, which is associated with a wide range of properties, such as antioxidant, anti-inflammatory, antiangiogenic, and antitumor activates. It exerts therapeutic effects via activation/inhibition cellular and molecular targets involved in various diseases, such as retinal diseases. Increasing evidence revealed that curcumin can be used as a therapeutic option in the treatment of different retinal diseases. Here, we summarized various clinical and preclinical studies that used curcumin as a therapeutic agent in the treatment of retinal disorders.

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Diagnosis & screening


Expanding the role of medical retina virtual clinics using multimodal ultra-widefield and optical coherence tomography imaging.
Lee JX, Manjunath V, Talks SJ.

Background: An increasingly elderly population with a corresponding increase in ophthalmic conditions has led to increased pressure on hospital eye services (HES). In this study, we evaluated the use of a
medical retina virtual clinic (MRVC), which has expanded into assessing all new medical retina referrals, where the need for urgent treatment was not clear.

Methods: Retrospective analysis of all new patients who were seen in the MRVC between April 2016 and May 2018. Pro forma sheets were used in the MRVC to record the patient history, visual acuity, and type of imaging required. Two consultants reviewed the completed pro formas and images and provided a final diagnosis and management plan. These results and reasons for face-to-face (F2F) clinic appointment requests were analyzed.

Results: Six hundred ten new referrals were enrolled in the virtual clinic. The most common diagnosis was diabetic eye disease (59.9%). In the virtual clinic 44.1% were followed up, 28.1% were discharged, and 27.8% were booked an F2F clinic appointment (urgent/routine). The main reason for F2F clinic was to offer treatment. Urgent F2F appointments took place on average 11.9 days after virtual clinic attendance. In only two cases was the image quality felt to be inadequate to assess the retina.

Conclusions: MRVC is an effective way of triaging medical retina referrals to allow those patients needing treatment to be seen promptly in the medical retinal service. The use of multimodal ultra-widefield and optical coherence tomography imaging allows assessment of a wide range of retinal pathologies and is a promising solution to alleviate the burden on HES.

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Drusen subtypes and choroidal characteristics in Asian eyes with typical neovascular age-related macular degeneration.


Purpose: To investigate the prevalence of pachydrusen, soft drusen, and subretinal drusenoid deposits in eyes with different neovascular age-related macular degeneration (nAMD) subtypes, determine the relationship between each drusen type and the choroidal thickness, and analyze the distinct features of each nAMD subtype according to the drusen type.

Methods: Medical records involving 454 eyes from 454 patients with nAMD were retrospectively reviewed. The prevalence of each drusen type and the choroidal thickness and choroidal characteristics were evaluated according to the nAMD subtype.

Results: Pachydrusen were prevalent in the typical nAMD (40.4%) and polypoidal choroidal vasculopathy (47.8%) groups and were not detected in the retinal angiomatous proliferation group. No significant drusen were detected in 24.3% of typical nAMD, 43.3% of polypoidal choroidal vasculopathy, and 0% of retinal angiomatous proliferation groups. Regardless of the nAMD subtype, pachydrusen, soft drusen, and subretinal drusenoid deposits were associated with a thick, moderately thick, and thin choroid, respectively. For eyes with typical nAMD, the prevalence of choroidal vascular hyperpermeability and extrafoveal neovascularization was significantly higher in the pachydrusen group than in the other groups. By contrast, the prevalence of Type 2 neovascularization was significantly lower in the pachydrusen group than in the subretinal drusenoid deposit group (P < 0.001 for all).

Conclusion: The prevalence of various drusen differed according to the nAMD subtypes, and each drusen type was strongly associated with the choroidal thickness. Typical nAMD showed distinct features according to the accompanying drusen type.

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Repeatability and reliability of quantitative fundus autofluorescence imaging in patients with early and intermediate age-related macular degeneration.
Reiter GS, Told R, Baratsits M, et al.

Purpose: Quantification of fundus autofluorescence has only recently become available. We report our findings on the evaluation of the repeatability and reliability of quantitative fundus autofluorescence (qAF) measurements in patients with early and intermediate age-related macular degeneration (AMD), using the first approved and commercially available instrument.

Methods: A total of 43 eyes of 22 patients (aged between 52 and 84 years) diagnosed with early and intermediate AMD were included. All eyes were imaged at day 1, 3 months and 6 months using a modified scanning laser ophthalmoscope, equipped with an internal fluorescent reference. Mean qAF values were calculated for the fovea and for each concentric ring of the Delori pattern. Repeatability and reliability were calculated using Bland-Altman analysis and intraclass correlation (ICC).

Results: The mean patient age was 73.5 ± 7.9 years. Sixteen patients (73%) were female. qAF repeatability of the eight segments in the middle ring of the Delori pattern (qAFM 8) for between sessions was ±8.2%. Agreement at 3- and 6-month follow-up in eyes without retinal changes was ±8.3% and ±9.8%, respectively. Reliability of qAFM 8 was high for all images acquired [ICC = 0.98 (CI: 0.96-0.99), 0.97 (0.93-0.99) and 0.98 (0.92-0.99)]. Agreement at 3- and 6-month follow-up in eyes with retinal changes was ±18.1% and ±20.2%, respectively. Intraclass correlation (ICC) was slightly lower in eyes with retinal changes at 0.93 (0.84-0.97) and 0.96 (0.91-0.98), respectively.

Conclusions: Quantitative autofluorescence shows excellent repeatability and reliability as well as follow-up agreement in patients with early and intermediate AMD without retinal changes. This is relevant when conducting longitudinal studies using qAF.

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Genetics & gene therapy

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Preclinical evaluation of ADVM-022, a novel gene therapy approach to treating wet age-related macular degeneration.


Abstract: Inhibition of vascular endothelial growth factor, a key contributor to the choroidal neovascularization associated with wet age-related macular degeneration, is the mode of action of several approved therapies, including aflibercept, which requires frequent intravitreal injections to provide clinical benefit. Lack of compliance with the dosing schedule may result in recurrence of active wet macular degeneration, leading to irreversible vision impairment. Gene therapy providing sustained anti-vascular endothelial growth factor levels in the retina following a single injection could drastically reduce the treatment burden and improve visual outcomes. ADVM-022, an adeno-associated virus vector encoding aflibercept, is optimized for intravitreal delivery and strong protein expression. Here, we report the long-term expression and efficacy of ADVM-022-derived aflibercept in a laser-induced choroidal neovascularization model in non-human primates. Intravitreal administration of ADVM-022 was well tolerated and resulted in sustained aflibercept levels. In addition, ADVM-022 administration 13 months before lasering prevented the occurrence of clinically relevant choroidal neovascularization lesions, similar to animals that received a bolus of intravitreal aflibercept (standard of care) at the time of lesioning. These results demonstrate that a single intravitreal administration of ADVM-022 may provide a safe and effective long-term treatment option for wet macular degeneration and may ultimately improve patients’ visual outcomes.

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Case reports

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**Cuticular drusen associated with aneurysmal type 1 neovascularization (polypoidal choroidal vasculopathy).**

Fragiotta S, Kaden TR, Freund KB.

**Background:** Aneurysmal type 1 neovascularization (AT1) is a term recently introduced to better describe the aneurysmal dilatation that may arise from neovascular lesions, more commonly known as polypoidal choroidal vasculopathy. The proposed term, AT1, includes an expanded clinical spectrum of aneurysmal (polypoidal) lesions observed in both different ethnicities and associated with varied clinical phenotypes.

**Case Presentation:** A 61-year-old woman of European descent was referred for a new, asymptomatic retinal hemorrhage found on routine examination. Ophthalmoscopy revealed cuticular drusen in both eyes best appreciated on fundus autofluorescence, and a hemorrhagic retinal pigment epithelium detachment above the superior arcade in the right eye. In the fellow eye, a reddish appearing pigment epithelial detachment was noted nasal to the optic nerve. Indocyanine green angiography showed findings of AT1 in both eyes. Optical coherence tomography angiography showed intrinsic flow signal within the aneurysmal lesions.

**Conclusions:** Eyes with cuticular drusen may develop AT1 which, to our knowledge, has not been described. This is an important observation because the documented coexistence of AT1 in the setting of a variant of age-related macular degeneration lends supports to this new understanding of AT1 as a growth pattern of neovascular tissue proliferating between the RPE and Bruch membrane, rather than as a distinct disease entity.