New Frontiers in Retina: highlights of the 2020 angiogenesis, exudation and degeneration symposium

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Abstract
We summarize the most important findings presented at the 2020 angiogenesis, exudation and degeneration symposium in five topic areas: (1) epidemiology of retinal vascular disease and macular degeneration; (2) dry AMD and geographic atrophy; (3) neovascular age-related macular degeneration; (4) drug delivery and devices and (5) diabetic retinopathy.

Keywords: Geographic atrophy, Neovascular AMD, Diabetic retinopathy, Imaging, Artificial intelligence

Background
The Angiogenesis, Exudation, and Degeneration Symposium has proven to be one of the most important meetings for the retina space [1]. The 16th annual meeting, sponsored by the Bascom Palmer Eye Institute, was held in Miami, Florida on February 8th, 2020. The program provides a comprehensive review of key new developments in retinal pharmacotherapy, including updates on new drugs and delivery systems aimed at improving treatment options for the early stages of age-related macular degeneration (AMD), the advanced stages of geographic atrophy (GA) and neovascular AMD (nAMD), and the many manifestations of diabetic retinopathy (DR) including diabetic macular edema (DME), proliferative DR (PDR) and non-proliferative DR (NPDR). Together, AMD and DR remain two of the greatest causes of visual disability in developed nations (2). Advances in imaging and optimization of artificial intelligence algorithms for guiding prognosis and management of both AMD and retinal vascular disease were also discussed and actively debated [2].

Within a framework of the major retinal diseases, the current manuscript highlights what we believe to be the most insightful, relevant and important topics for the vitreoretinal community to recognize at the dawn of a new decade.

Epidemiology of retinal vascular diseases and macular degeneration
Dr. Andrew Moshfeghi reported on the epidemiology of the diseases managed in retinal practices across the United States from 2014 to 2019 by evaluating the electronic medical records of more than 300 retinal specialists. Eyes with either a retinal vascular disease or AMD accounted for more than half of all eyes evaluated and the prevalence of both increased across the 6-year period. The prevalence of specific retinal diseases included 16% with the early, intermediate or late stages of dry AMD; 13% with neovascular AMD (nAMD); 10% with diabetic macular edema (DME); 8% with diabetic retinopathy without DME; 3% with branch retinal vein occlusion (RVO); 2% with central RVO.

Dry AMD and geographic atrophy
The dry forms of AMD, in particular GA, remain the largest unmet need in retinal disease management [3] and many of the ongoing clinical trial programs, including 2
of which are currently being investigated in global phase 3 programs, were described in detail. Two study programs focused on earlier stages of dry AMD and highlighted the under-appreciated need for considering the visual dysfunction such patients experience.

Dr. Scott Cousins provided an update of the ReCLAIM Trial which investigated the use for elamipretide (Stealth BioTherapeutics, Cayman Islands) for the treatment of vision loss associated with intermediate dry AMD and noncentral GA. Elamipretide, a mitochondrial protective drug, is hypothesized to improve vision and dark adaption in dry AMD. Eyes with either noncentral GA or high risk drusen with BCVA ≥ 55 letters and low luminance deficit were treated with 40 mg of elamipretide subcutaneously once daily for 24 weeks. Exploratory endpoints included change in BCVA, low luminance visual acuity (LLVA) and low luminance reading acuity (LLRA). In the drusen cohort, BCVA improved 3.6 ± 6.4 letters (p = 0.025) and LLVA improved 5.6 ± 7.8 letters (p = 0.006). In the noncentral GA cohort, GA area growth was reduced 50% compared to historical controls. Dark adaption (DA) is a difficult outcome to quantify due to variability in disease severity, patient effort and methodology. In spite of these limitations, results were suggestive elamipretide therapy can improve DA in some subjects. In the drusen cohort dark adaption improved at 2 or more visits in 47% of eyes and in the noncentral GA cohort in 38% of eyes. Elamipretide continues to be studied in ongoing human clinical trials [4].

Dr. Glenn Jaffe and Dr. Peter Kaiser presented results from a Phase 2 trial of risuteganib (Luminate, Allegro Ophthalmics, San Juan Capistrano, CA). The study suggested that some of the structural changes observed in dry AMD may be able to be ameliorated with an associated improvement in visual function [5]. Risuteganib is a synthetic oligopeptide purported to regulate select integrin functions involved in the pathogenesis of dry AMD. In preclinical studies, risuteganib protected retina cells against cytoxins such as peroxide. Forty-five patients with a wide range of phenotypes of dry AMD and best corrected VA (BCVA) between 20/40 and 20/200 were treated with either intravitreal 1.0 mg risuteganib or sham injection. A key inclusion criteria was symptomatic decrease in VA over the past year. At week 16, patients in the risuteganib group received a second 1.0 mg risuteganib dose. Outcomes from the active treatment arm at week 28 were compared to outcomes from the control arm at week 12, an unusual study design. A gain of ≥ 8 letters from baseline was observed in 48% of active treated patients at week 28 vs 7% of sham patients at week 12. A gain of gained ≥ 15 letters was observed in 20% of active treated patients at week 28 vs no sham patients at week 12. By OCT analysis, greater outer retinal and photoreceptor thickness and volume and smaller ellipsoid zone defects within the central 1 mm zone at baseline were associated with increased BCVA response to risuteganib. A larger, randomized, masked study (estimated to be approximately 345 patients) is planned to study the proportion of patients gaining ≥ 15 letter gain as the primary endpoint.

Dr. Cedric Francois presented new observations regarding the pathogenesis of exudative AMD (E-AMD) noted in 11% of eyes in the Phase 2 FILLY trial of peg-fetacoplan (APL-2; Apellis, Crestwood, KY), an inhibitor of C3 cleavage [6]. APL-2 appears to be one of the most promising agents for treatment of GA and is being studied in a global phase 3 program involving an estimated 1200 patients [7]. The hypothesis described is that C3 breakdown products including C3b can overload the retinal pigment epithelium (RPE) causing an energy deficit leading to cellular dysfunction and subsequent photoreceptor injury and death. In the Phase 2 trial involving 246 subjects, eyes were treated with intravitreal injections of 15 mg/0.1 ml of APL-2 monthly (M) or every other month (EOM) for 12 months, with GA growth being reduced by 20% and 29% in the EOM and M groups respectively. One unexpected finding from the FILLY trial was the development of investigator-determined E-AMD occurred in 9% and 21% of eyes in EOM and M groups respectively. History of nAMD in the contralateral eye at baseline was a risk factor for development of study eye E-AMD. Specifically, 69% of eyes that developed E-AMD had a history of fellow eye nAMD compared to 33% of eyes not developing E-AMD. Furthermore, retrospective review of baseline OCT data found that 73% of eyes that developed E-AMD had the "double layer sign", compared to 32% of treated eyes that did not develop. The "double layer sign" has been observed to be associated with quiescent type 1 CNV [8]. The authors speculated that APL-2 may increases exudation from preexisting type 1 CNV. This observation suggests that pretreatment OCT angiography to identify type 1 CNV might be useful in identifying eyes at greater risk for developing E-AMD and thus might benefit from closer clinical monitoring. Importantly, with prompt anti-VEGF treatment, VA did not appear to be negatively affected among eyes developing E-AMD compared to eyes not developing E-AMD.

Dr. Carl Csaky reported data from a pivotal clinical trial of avacincaptad pegol (Zimura, IVERIC bio, New York, NY), an aptamer that inhibits C5 cleavage, for the treatment GA [9]. Prevention of C5 cleavage is projected to prevent inflammamson activation through C5a and prevent membrane attack complex (MAC) formation through C5b. A total of 286 subjects were treated with monthly intravitreal injection of avacincaptad pegol (2 mg and 4 mg study arms) or sham injection [10]. The
primary efficacy endpoint was the mean rate of change of GA over 12 months measured by fundus autofluorescence at three time points: baseline, month 6 and month 12 using a square root transformation of GA area to account for differences in growth rates due to difference in baseline lesion size, a well-accepted approach also used in FILLY. The primary efficacy endpoint was achieved for both the 2 mg and 4 mg doses, leading to approximately a 27% reduction in GA growth through 12 months. Development of nAMD was reported in 2.7% of sham eyes compared to 9-10% of the avacincaptad treated patients. A Phase 3 trial studying the 2 mg dose is anticipated.

Dr. Ryan Rich reported results of two Phase 2 studies using a sustained release brimonidine implant (Brimo DDS, Allergan, Irvine, CA) for treatment of eyes with GA. Preclinical studies involving RPE and Muller cells have demonstrated cytoprotective effects with brimonidine. The first trial investigated Brimonidine doses of 132 and 264 Å µg compared to sham among 113 patients; at the 12-month time point, the brimonidine treated eyes demonstrated reduced GA growth by 19% and 28% in the 132 and 264 brimonidine arms compared to sham. In a second trial involving a 400 Å µg implant [11], the GA growth rate was reported to be reduced by 7% and 11% at the 24- and 30-month time points compared to sham. Overall the beneficial effect of brimonidine was more robust among eyes with larger areas of GA at baseline and there was no indication of increased nAMD development in the active treatment groups. The possibility of moving forward into a phase 3 program was discussed.

Dr. Vrinda Hershberger reported results from a Phase 1 trial of GR39821 among patients with GA (Genentech, South San Francisco, CA), a single ascending, multiple-dose study evaluating the safety and tolerability of an intravitreally delivered therapeutic designed to inhibit anti-High Temperature Requirement A1 (HtrA1) [12]. Genome wide association studies have identified ARMS2/HTRA1 to be a significant locus impacting AMD risk [13]. HtrA1 is a secreted protease expressed by RPE and horizontal cells that degrades extracellular matrix proteins as well as proteins involved in the visual cycle. Inhibition of HtrA1 is hypothesized to slow the progression of GA lesion growth. The Phase 1 study found that intravitreal anti-HtrA1 was well tolerated at doses up to 20 mg/eye, with no dose-limiting toxicities, ocular serious adverse events (AEs), or systemic or ocular AEs related to the anti-HtrA1 pharmaceutical. Furthermore, aqueous humor analyses suggested on target activity of the agent and suggested duration of effect greater than 8-weeks with the higher doses. A phase 2 study of is enrolling.

OCT-A continues to grow as a research tool and is now well-accepted as an important clinical tool in the evaluation of eyes with AMD. Imaging of the choriocapillaris in attempt to understand the role of vascular perfusion in the pathogenesis of AMD is a topic of intense investigation. Dr. Ricky Wang performed volumetric imaging of the choroidal vasculature using swept source (SS) OCT-A and reported that choroidal volume varies widely in normal subjects, the choroid thins with increasing age, and that choroidal vessel density appears independent of age in normal subjects. Dr. Philip Rosenfeld is exploring the role of the choriocapillaris (CC) in AMD progression. Challenging this field, however, drusen cast shadows on the underlying CC and these can interfere with CC flow measurements by OCT-A [14]. In this study, a novel compensation strategy to overcome the effect of these drusen-associated shadows was developed and the strategy was validated by imaging eyes with drusen and shadows and then again after drusen spontaneously collapsed without development of GA, so that no shadows remained.

Dr. Emily Chew discussed the development of a deep learning algorithm to detect features of AMD including drusen, reticular pseudodrusen (RPD), pigmentary changes as well as both forms of late AMD. DeepSeeNet [15] is an artificial intelligence (AI) system designed to assign eyes to a specific AREDS severity scale based on evaluation of color fundus photographs of drusen (by size, small, medium or large) and presence of pigmentary changes, two validated biomarkers for the risk of progression to late AMD at a patient level. This system performed better than clinicians in detecting drusen and pigmentary changes but was inferior to clinicians in the detection of late AMD. Larger training sets may be able to improve DeepSeeNet performance.

**Neovascular age-related macular degeneration**

Most exudative retinal diseases are chronic and relapsing, and while treatable with anti-vascular endothelial growth factor (VEGF) medications, they require repeated therapeutic interventions over years, often indefinitely. It has been estimated that in 2019, a total of 24.4 million intravitreal injections were administered globally, with 6.9 million of these injections performed in the United States alone. Developing drugs, devices, and strategies that can reduce this tremendous treatment burden are a priority. Promising approaches include (a) new anti-VEGF-A monotherapies with extended duration of intraocular biological activity, (b) combination approaches targeting cytokines and relevant molecular pathways beyond VEGF-A. (c) novel delivery systems, and (d) gene therapy with the goal of establishing an intra-ocular bio-factory to produce an anti-VEGF protein continuously.

Dr. Diana Do presented an update related to an ongoing, open label, Phase 1b study of a next-generation
intravitreal anti-VEGF agent, KSI-301 (Kodiak Sciences, Palo Alto, CA). KSI-301 is an antibody biopolymer conjugate, meaning a novel full-length antibody against all forms of VEGF-A is covalently linked to an optically clear, branched, high molecular weight phosphorylcholine biopolymer via a single site-specific stable linkage. This approach leverages a larger size (950 kDa) with a 5 mg clinical dose in attempt to achieve extended intraocular duration of action. In comparison, aflibercept (Regeneron Pharmaceuticals, Tarrytown, NY) has a molecular weight of 115 kDa and a clinical dose of 2 mg. Preclinical modeling suggests that KSI-301 may be able to achieve an intraocular concentration at 3 months that is 1000 times greater than that of aflibercept. 130 patients (wAMD, n = 50; DME, n = 35; and RVO, n = 35) were randomized to 2 doses of KSI-301 and after 3 monthly loading doses, eyes were monitored monthly with protocol guided retreatment [16]. Impressively, among the wAMD arm 55% of eyes were reported to achieve a 6-month interval before a mandated first retreatment with 84% of eyes going 4 months or longer without retreatment. At 24 weeks (with a mean of 0.16 injections between weeks 8 and 24), BCVA had improved 5.9 letters compared to baseline. In the DME arm, 64% of eyes reached 6 months or longer without retreatment. In the RVO arm, 53% reached 4 months or longer without retreatment. No intraocular inflammation or ocular SAEs were reported in study eyes to date. A Phase 2, pivotal nAMD trial randomizing patients to aflibercept vs KSI-301 is underway [17].

Dr. Barry Kupperman reported results related to abicipar pegol for the treatment of nAMD (Allergan). Abicipar was engineered using DARPin technology in attempt to generate a novel anti-VEGF agent with high binding affinity. In the phase 3 CEDAR and SEQUOIA trials [18], the proportion of eyes with stable vision, losing less than 15 letters, was reported to be similar between eyes treated with abicipar every 8 weeks, abicipar every 12 weeks, and ranibizumab (Genentech) every 4 weeks through both 1 and 2 years of dosing. The biggest challenge appears to be inflammation. In the phase 3 program, the overall incidence of intraocular treatment emergent adverse events was about 15% in the abicipar arms compared 0.3% in the ranibizumab arm from baseline through week 52. Concerningly, a meaningful proportion of patients treated with abicipar who developed intraocular inflammatory events developing occlusive vasculitis. In a subsequent prospective trial, MAPLE, which used abicipar manufactured using a modified process, the overall incidence of inflammation was reported to decrease to 8.9% through 28 weeks of treatment and most events were reported to be mild to moderate in severity.

Combination therapies targeting angiopoietin-2 (ANG2) or VEGF-C and VEGF-D in addition to VEGF-A may allow improvement in visual and anatomic outcomes beyond VEGF-A monotherapies. Dr. Karl Csaky provided an update on clinical studies employing faricimab (Genentech) which is the first bispecific antibody designed for intraocular use [19], capable of simultaneously inhibiting both VEGF-A and angiopoietin 2 (ANG2). Faricimab has demonstrated sustained inhibition of both VEGF-A and ANG2 in human studies with evidence of increased durability beyond the effect of ranibizumab monotherapy in both DME [20] and nAMD phase 2 studies. The Phase 2 Stairway Trial demonstrated the potential for faricimab q 16-week dosing for the management of nAMD; 3 arms were studied: ranibizumab 0.5 mg every 4 weeks; faricimab 6 mg every 12 weeks and faricimab 6 mg every 16 weeks. BCVA at 52 weeks was equivalent for all 3 arms with 65% of faricimab eyes demonstrating no prespecified evidence of disease activity at week 24, 12 weeks after the last faricimab loading dose. Phase 3 trial programs in both nAMD and DME have been fully enrolled with anticipated data within the next year for the nAMD trials [20, 21].

Dr. Pravin Dugel presented the results of a Phase II clinical trial studying the use of OPT-302 (Opthea, South Yarra, Victoria, Australia) in combination with ranibizumab for the treatment of nAMD. OPT-302 (sVEGFr) is a “trap” inhibitor of VEGF-C and VEGF-D, which typically signal through VEGFR-2 and VEGFR-3. Currently used anti-VEGF agents (ranibizumab, bevacizumab (Genentech), aflibercept, and brolucizumab (Novartis, Basel, Switzerland) inhibit VEGF-A or VEGF-A, B and placental growth factor (aflibercept). This study hypothesized that pan-VEGF blockade would improve clinical outcomes. The trial included three treatment arms: 2.0 mg OPT-302 plus 0.5 mg ranibizumab; 0.5 mg OPT-302 plus 0.5 ranibizumab; 0.5 ranibizumab plus sham. All 3 arms received 6 monthly doses. Patients in the 2.0 mg OPT-302 plus 0.5 mg ranibizumab group gained a mean of 14.2 letters of vision from baseline compared to 10.8 letters in the ranibizumab monotherapy group (p = 0.0107) [22]. Progression into a global phase 3 program was discussed.

In addition to the development of new pharmaceutical agents that inhibit VEGF-A and other cytokines as described above, there are also promising drives to improve delivery of our current pharmaceutical agents. The port delivery system (PDS, Genentech) utilizes a hardware approach to sustained delivery of ranibizumab. Gene therapy is also being pursued in which viral vectors are used to create an intraocular bio-factory for the production of either aflibercept or ranibizumab.
Dr. Carl Regillo presented end-of-study results of the Ladder phase II trial which studied the PDS in nAMD management [23]. The PDS is a transscleral device which is surgically implanted at the pars plana that serves as a refillable intraocular reservoir allowing continuous delivery of ranibizumab by diffusion. The PDS can be refilled in clinic using a proprietary flushing-syringe by accessing the PDS through the overlying conjunctiva and Tenon’s layer. In the PDS 100 mg/ml arm of Ladder, approximately 80% of patients went ≥ 6 months and approximately 60% went ≥ 12 months without meeting pre-defined specific refill criteria. In patients who received ≥ 1 refill, median time to first and second refills was consistent at about 8.8 months. Top-line serum pharmacokinetic data appeared to support that the PDS was consistent at about 8.8 months. Top-line serum nAMD conversion rate. In eyes with non-exudative to enrollment in ProCon was associated with a higher history of nAMD diagnosis in a fellow eye (n = 63) and 10.9% (n = 64) in the sham group. A history of nAMD diagnosis in a fellow eye ≤ 2 years prior to enrollment in ProCon was associated with a higher nAMD conversion rate. In eyes with non-exudative CNV as demonstrated by OCT angiography (OCT-A) at baseline, the rates of nAMD conversion were meaningfully higher (27% in the treated group and 31% in the sham group). Development or progression of GA was not affected by quarterly aflibercept treatment. The conclusion of this 2-year study supports the current management consensus that anti-VEGF dosing be initiated after exudation develops, with the consideration that once exudation manifests, earlier treatment leads to better absolute outcomes [29].

Dr. Anat Loewenstein presented updates on the development of a low-cost, AI-enabled, patient self-operated home OCT system (Notal Vision, Manassas, VA). It had been previously reported that patients could successfully self-image with the Home OCT prototype device, and graders could identify retinal fluid with 98% sensitivity and 97% specificity in these Home OCT images when compared to images taken with a commercial device. This year, the final device configuration was shown, with examples of image quality for fluid identification which were consistent with the Spectralis device. A deep learning algorithm, the Notal OCT Analyzer (NOA) was used to identify minute quantities of intra and sub-retinal fluid, on the nano-liter scale, which were also represented in fluid thickness maps. A longitudinal analysis was performed on a patient, and the algorithm was able to detect amounts as small as 18 pico-liters. The patient self-testing with the Home OCT demonstrated the longitudinal disease dynamics, with the detection of a 7× increased amount of fluid within 4 days to 124 nl, and subsequent resolution of 3x within 3 days followed by continuous resolution after treatment with anti-VEGF therapy. The information generated by tele-connected OCT in patients’ homes has the potential to support current and future advances and retinal disease management.

**Drug delivery and devices**

Suprachoroidal approaches continue to be investigated as a route for therapeutics targeting retinal diseases. Dr. Thomas Albini reviewed the use of a proprietary micro-injector (Clearside Biomedical, Alpharetta, Georgia, USA) for precise delivery into the suprachoroidal space (SCS). There are multiple theoretical advantages with suprachoroidal delivery: (a) targeting the therapeutic effect to the retina and choroid while minimizing exposure to anterior segment structures such as the filtration angle and crystalline lens and (b) no entry into the vitreous cavity is required. The Phase 3 Peachtree trial [30] demonstrated the safety and efficacy of this system for delivering triamcinolone acetate (TA) for the treatment of cystoid macular edema secondary to uveitis. In contrast to what would be expected with intravitreal delivery of TA, there was a lower signal of intraocular pressure...
increase and cataract development following suprachoro
doidal delivery. Suprachoroidal delivery of a gene therapy
has also been reported to achieve similar expression of an
anti-VEGF Fab as achieved with subretinal delivery with
Corresponding functional suppression of vascular leakage
[31].

**Diabetic retinopathy**

Dr. Charles Wykoff presented 2-year results from the
phase III, double-masked PANORAMA trial that random-
omized treatment-naïve eyes with moderately severe to
severe NPDR without center-involved DME (n=402)
to either sham or 2 dosing regimens of aflibercept. In
the 2nd year, the every 4-month (Q16) aflibercept arm
continued fixed Q16 dosing and maintained the propor-
tion of patients who achieved an improvement of two or
more diabetic retinopathy severity scale (DRSS) steps at
about 62% with a mean of just 2.6 injections. In compari-
sion, in the 2nd year the every 2-month (Q8) aflibercept
arm transitioned to PRN re-treatment based on inves-
tigator determined DRSS level; using this approach, the
proportion of patients who achieved an improvement of
two or more DRSS steps decreased from 80% at 1 year
to 50% at 2 years. Of primary clinical relevance, using a
Kaplan–Meier analysis accounting for discontinued pa-
teints, nearly 58% of sham eyes developed either PDR
or CI-DME by the end of year 2, a proportion reduced by
about 75% with aflibercept dosing using either approach
to about 19% [32].

Dr. Harry Flynn described the use of wide-field (WF)
OCT-A in the diagnosis and follow-up care of eyes with
proliferative DR (PDR). OCT-A was found to be as effec-
tive as, or even more effective than, WF fluorescein angi-
ography (FA) for identifying and following both areas of
neovascularization as well as areas of retinal non-perfu-
sion in and near the posterior pole. The added value of
WF-FA imaging was the inclusion of more far-peripheral
pathology than was captured using OCT-A along. High
speed SS-OCT coupled with software montage tech-
niques provided the highest quality WF images. Future
clinical studies involving DR should consider using both
SS-OCT-A and WF-FA as relevant clinical endpoints.

Dr. Michael Ip discussed utilization of AI for DR
screening and presented the results for the EyeArt
(Eyenuk, Inc, Woodland Hills, CA, USA) multicenter
prospective clinical trial. Current approach to screen-
ing patients with diabetes mellitus for DR in the United
States are not achieving adequate penetration. This study
assessed the sensitivity and specificity of the EyeArt sys-
tem in detecting referable DR and vision threatening DR
by analyzing 2-field non-mydriatic fundus photographs.
The clinical reference was standardized, adjudicated DR
grading performed by the Wisconsin Fundus Photograph
Reading Center. The EyeArt system, with no pupillary
dilation, achieved a remarkable sensitivity of 95.5%, less
impressive specificity at 86.0% and gradeability of 87.5%.
This study demonstrated that the EyeArt system may be
able to be used to improve rates of DR screening and may
be valuable in assisting our health care system at identify
and triaging patients requiring ophthalmology evalua-
tion and possible intervention for this largely preventable
cause of blindness.

**Conclusions**

There remains a tremendous amount of activity in the
space of research targeting the development and refine-
ment of therapeutics for retinal diseases. The 2020
Angiogenesis, Exudation and Degeneration Symposium
highlighted some of the most promising innovations shap-
ing the landscape of clinical research in retinal dis-
eases. Both the intermediate and advanced forms of dry
AMD remain an enormous un-met need, and multiple
therapeutics including elamipretide, risuteganib, pegc-
etacoplan, avacincaptad, brimonidine and GR39821
are being explored for potential benefit in this arena.
Novel pharmaceutical agents including KSI-301, abici-
par, faricimab and OPT-302 are being investigated for
their capacity to improve efficacy and durability beyond
our current anti-VEGF monotherapies. Gene therapy
approaches in ADVM-022 and RGX-314 as well as sur-
gical devices such as the PDS and are being pursued for
their promise of delivering more durable anti-VEGF
activity. Woven into these development programs and
promising to improve prognostication are improved
imaging systems and validated AI algorithms.

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References

1. Puliafito CA, Wykoff CC. Looking Ahead in Retinal Disease Management: highlights of the 2019 angiogenesis, exudation and degeneration symposium. International Journal of Retina and Vitreous. 2019 May 29 (Epub ahead of print).

2. Taylor HR, Keeffe JE. World blindness: a 21st century perspective. Br J Ophthalmol. 2001;85(3):261–6. https://doi.org/10.1136/bjo.85.3.261.

3. Holekamp N, Wykoff CC, Schmitz-Valckenberg S, et al. Natural history of geographic atrophy secondary to age-related macular degeneration: results from the prospective proxima A and B clinical trials. Ophthalmology. 2019. https://doi.org/10.1016/j.jophtha.2019.12.009.

4. ClinicalTrials.gov Identifier: NCT03891875.

5. ClinicalTrials.gov Identifier: NCT03626636.

6. Liao DS, Grossi FV, El Mehdi D, Gerber MR, Brown DM, Heier JS, Wykoff CC, Singerman LJ, Abraham P, Grassmann F, Nuernberg P, Weber BHF, Deschatelets P, Kim RY, Chung CY, Ribeiro RM, Hamdani M, Rosenfeld PJ, Boyer DS, Slakter JS, Francois CG. Complement C3 Inhibitor Pegcetacoplan for Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Randomized Phase 2 Trial. Ophthalmology. 2019 Jul 16 (Epub Ahead of Print).

7. ClinicalTrials.gov Identifier: NCT03525600.

8. de Oliveira Dias JR, Zhang Q, Garcia IMB, et al. Natural History of Subclinical Neovascularization in Nonexudative Age-Related Macular Degeneration Using Swept-Source OCT Angiography. Ophthalmology. 2018;125(2):255–66. https://doi.org/10.1016/j.jophtha.2017.08.030.

9. https://www.businesswire.com/news/home/20191028005259/en/IVERIC-C-bio%E2%80%99s-Zimura%C2%AE-Complement-C5-Inhibitor-Met.

10. ClinicalTrials.gov Identifier: NCT02087086.

11. ClinicalTrials.gov Identifier: NCT03295877.

12. Yang Z, Camp NJ, Sun H, Tong Z, Gibbs D, Cameron DJ, et al. A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. Science. 2006;314:992–3.

13. Chu Z, Cheng Y, Zhang Q, et al. Quantification of chorionicapillaris with Phansalkar’s local thresholding: pitfalls to avoid. Am J Ophthalmol. 2020. https://doi.org/10.1016/j.ajo.2020.02.003.

14. Peng Y, Dharsi S, Chen Q, et al. DeepSeeNet: a Deep Learning Model for Automated Classification of Patient-based Age-related Macular Degeneration Severity from Color Fundus Photographs. Ophthalmology. 2019;126(4):565–75. https://doi.org/10.1016/j.jophtha.2018.11.015 (ClinicalTrials.gov Identifier: NCT03799082).

15. ClinicalTrials.gov Identifier: NCT04049266.

16.  Khurana R. Abicipar for Neovascular AMD: Two-Year Results from CEDAR and SEQUOIA Phase 3 Clinical Trials. American Academy of Ophthalmology, Retina Subspecialty Day, October 11, 2019.

17. Regula JT, Lundh von Leitner P, Foston R, et al. Targeting key angiogenic pathways with a bispecific CrossMab optimized for neovascular eye diseases [published correction appears in EMBO Mol Med. 2019 May;11(5)]. EMBO Mol Med. 2016;8(11):1265–1288. Published 2016 Nov 2. https://doi.org/10.15252/emmm.201505889.

18. Sahnii J, Patel SS, Dugel PU, et al. Simultaneous Inhibition of Angiopoietin-2 and Vascular Endothelial Growth Factor-A with Faricimab in Diabetic Macular Edema: BOULEVARD Phase 2 Randomized Trial. Ophthalmology. 2019;126(8):1155–70. https://doi.org/10.1016/j.jophtha.2019.03.023.

19. ClinicalTrials.gov Identifier: NCT03622580.

20. https://www.globenewswire.com/news-release/2019/09/06/1912077/0/en/Ophthea-Presents-Positive-Data-from-DPT-302-Phase-2b-Wet-AMD-Trial-at-EURETINA-Congress.html.

21. Campochiaro PA, Marcus DM, Awkh CC, et al. The Port Delivery System with Ranibizumab for Neovascular Age-Related Macular Degeneration: results from the Randomized Phase 2 Ladder Clinical Trial. Ophthalmology. 2019;126(8):1141–54. https://doi.org/10.1016/j.jophtha.2019.03.036.

22. ClinicalTrials.gov Identifier: NCT03877934.

23. ClinicalTrials.gov Identifier: NCT04108156.

24. RGC-314 gene therapy for neovascular AMD trial. ClinicalTrials.gov Identifier: NCT03066258.

25. ADVM-022 gene therapy for wet AMD (OPTIC). ClinicalTrials.gov Identifier: NCT03748784.

26. ClinicalTrials.gov Identifier: NCT02462889.

27. Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. The neovascular age-related macular degeneration database: multicenter study of 92,976 ranibizumab injections: report 1: visual acuity. Ophthalmology. 2014;121(5):1092–1101. https://doi.org/10.1016/j.ophtha.2013.11.031.

28. ClinicalTrials.gov Identifier: NCT02593998.

29. Ding K, Shen J, Haftz Z, et al. AAV8-vectored suprachoroidal gene transfer produces widespread ocular transgene expression. J Clin Invest. 2019;130(11):4901–13. https://doi.org/10.1172/jci92085.

30. ClinicalTrials.gov Identifier: NCT02718326.

31. Motulsy EH, Liu G, Shi Y, et al. Wdefield swept-source optical coherence tomography angiography of proliferative diabetic retinopathy. Ophthalmic Surg Lasers Imaging Retina. 2019;50(8):474–84. https://doi.org/10.3928/23258160-20190806-01.

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