What's New in Medical Retina?

Chaitra Jayadev, MS, **Ram Snehith,** MS, **Arpitha Pereira,** MS
Narayana Nethralaya Eye Institute, Bangalore

It is said that things move fast in the world of modern medicine. The field of medical retina appears to be no exception, with numerous developments taking place, such as introduction of new drugs, new treatment modalities and imaging techniques. While a detailed description is out of the scope of this article, we hope to give you a glimpse into what is new in the world of medical retina.

Newer Imaging Modalities: We describe a few imaging modalities that have become popular recently.

1. Wide-field Imaging: Conventional fundus imaging typically generates images with a 30 to 50-degree field of view, corresponding to approximately 5% to 15% of the retinal surface area. This allows for visualization of the posterior pole but not theretinal periphery. The Optos system (Optos, Dunfermline, Scotland), through the use of a large ellipsoid mirror with 2 focal lengths (allowing wide scanning angles) and an SLO, provides image capture with a 200 degrees internal field of view (approximately equivalent to 135 to 150 degrees external field of view).The system provides the ability to capture red and green reflectance imaging, as well as fundus autofluorescence, and fluorescein/indocyanine green angiography.[1] Ultra-Wide-field Angiography (UWFA) has been shown to demonstrate abnormalities in a variety of retinal conditions, including diabeticretinopathy, retinal vein occlusion, sickle cellretinopathy, uveitis, and pediatric retinal disease.[2,3]

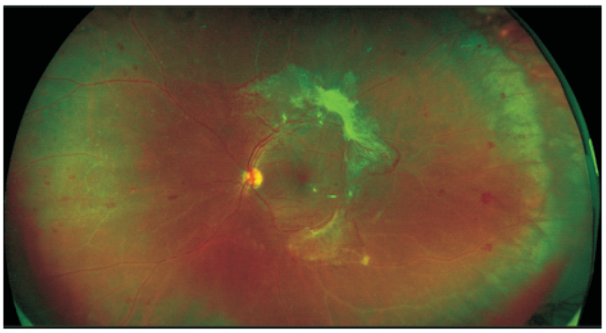

Figure 1 Wide-field Optos image of the left eye with advanced PDR showing extensive fibrovascular proliferation over the posterior pole and peripheral sclerosed vessels

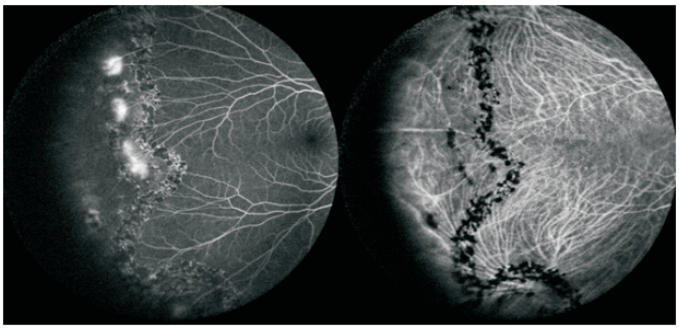

Figure 2 Wide field combined fundus fluorescein and indocyanine green angiography on the Spectralis platform in a 30-year-old male patient demonstrating peripheral vascular leak

2. Multi Color Imaging : Mult iColor scanning laser imaging is a new technology for fundus imaging offering detail and clarity not available from traditional fundus photography. Multi Color images are captured by simultaneously scanning with three individual laser wavelengths: blue, green, and infrared. The different wavelengths penetrate the tissue to different depths and therefore provide structural information from different depths within the retina.[4]

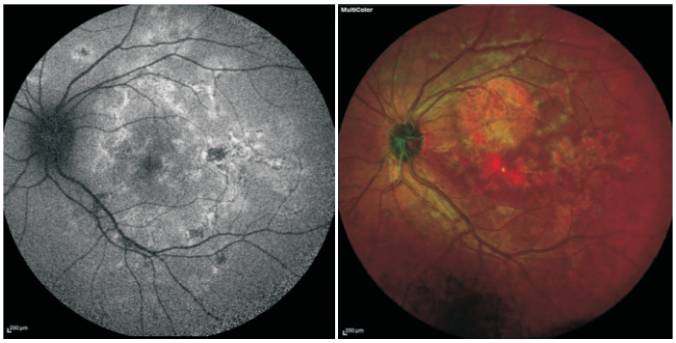

Figure 3Multicolor OCT image of the left eye showingserpiginous like choroiditis lesions in a 22-year-old male patient with the corresponding left eye autofluorescence image

3. Wide Field OCT : Optovue (Fremont, CA) Avanti RTVue-XR widefield system uses SD technology and can obtain 70,000 A-scans/second. The Avanti RTVue-XR can create 12 mm x 9 mm B-scans, and its active eye tracking enhances image stability. Wide field OCT can provide detailed information of the lesions that are present away from the arcade. These are very useful imaging modalities for conditions like choroidal tumors and peripheral lesions such as retinoschisis.[5-7]

4. Hand Held OCT: Spectral-domain OCT systems (Bioptigen EnvisuSDOIS; Bioptigen, Research Triangle Park, NC, USA) with handheld imaging probes connected to a table-topconsole by a 1.3-m-long cable is a device which has now been used widely in imaging pediatric disorders. It has been proven particularly useful in neonatal populations for the study of ocular development and for diseases such as retinopathy of prematurity.[8]

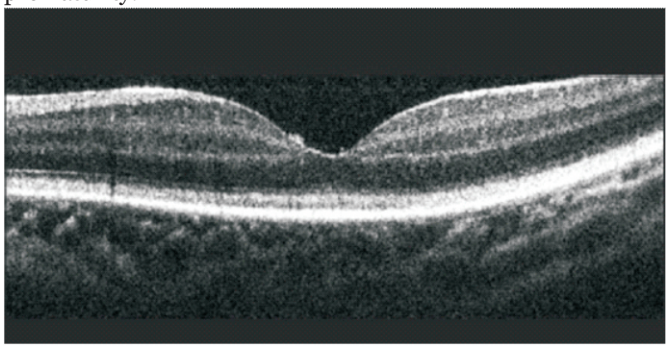

Figure 4A spectral domain-optical coherence tomography image using the Envisu 2300 (Bioptigen Inc., Research Triangle Park, NC, USA) of a 1-year old female child with a cone-rod dystrophy demonstrating an absent foveal tent and an irregularly thickened and hyper-reflective layer of cone outer segment tips

5. Adaptive optics: Optical retinal imaging modalities rely on the optical elements of the eye itself (mainly the cornea and lens) to produce retinal images. As a results of imperfections in these structures, aberrations are introduced to the imaging light and image quality is degraded. To compensate for these aberrations, adaptive optics (AO) along with optical coherence tomography (OCT) have been utilized.[9] This enabled for the first time invivo volumetric retinal imaging with high isotropic resolution. Using adaptive optics, photo receptor loss/changes can be imaged.[10,11]

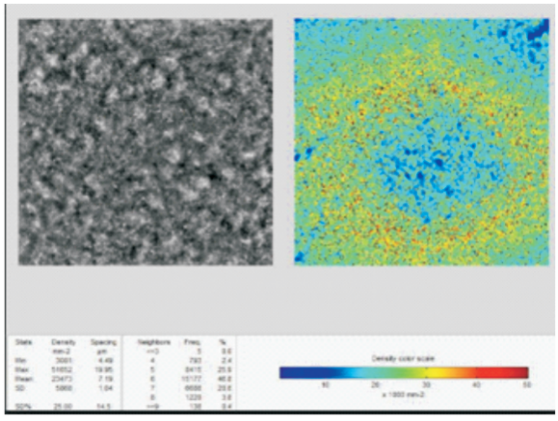

Figure 5 Adaptive optics imaging of the left eye fovea of a healthy 25-year-old male showing normal average cone count and distribution

6. Optical coherence tomography angiography (OCTA): OCTAis a new non-invasive imaging technique that employs motion contrast imaging to high-resolution volumetric blood flow information generating angiographic images in a matter of seconds. OCTA compares the decor relation signal (differences in the back scattered OCT signal intensity or amplitude) between sequential OCT b-scans taken at precisely the same cross-section in order to construct a map of blood flow. The two main types of OCTA instruments are spectral-domain OCTA (SD-OCTA) and swept-source OCTA (SS-OCTA). Both use Fourier domain detection techniques, but the SD-OCT instruments use a broadband near-infrared super luminescent diode as a light source, currently with a center wavelength of approximately 840 nm, with a spectrometer as the detector, while SS-OCT devices use a tunable swept laser while SS-OCT devices use a tunable swept laser, currently with a center wavelength of approximately 1,050 nm, with a single photodiode detector. The main advantage of SS-OCTA imaging over SD-OCTA is a faster scanning speed, which allows for denser scan patterns and larger scan areas than SD-OCTA scans for a given acquisition time. Another advantage of the current SS-OCTA technology is that it uses a longer center wavelength that can reduce sensitivity roll-off of the signal under the RPE, which results in enhanced light penetration into the choroid and better detection of signals from the deeper layers. [12,13]

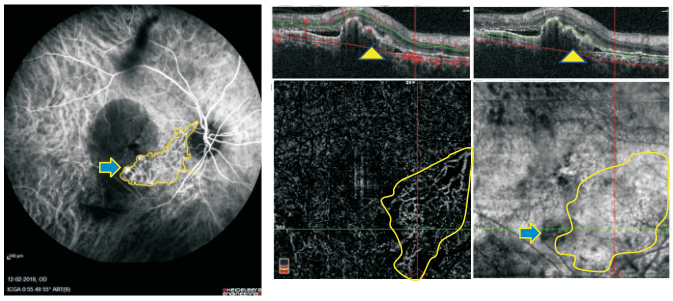

Figure 6A Indocyanine greenangiography of the right eye of a 55-year-oldmale patient, demonstrating a branched vascular network with hypercyanacent lesions at their terminal ends suggestive ofpolyps (highlighted).

Figure 6B SD OCTA image of the same eye delineating the outline of the branched vascular network.

New treatment options:

Age Related Macular Degeneration (AMD)

While tremendous progress has been made in the field of wet AMD, there still appears to be no treatment for dry AMD. Here, we take a look at some treatment options which may become viable in the near future

1. Photo biomodulation involves application of visible to near-infrared light to cells to produce beneficial effects. A recent study on 42 patient with dry AMD showed that application of multi-wavelength light composed of yellow (590 nm), red (670 nm) and near-infrared (790 nm) for a period of 3 weeks resulted in significant improvement in BCVA, contrast sensitivity, and the drusen size.[14]

2. Brimonidine is a selective alpha-2 receptor adrenergic agonist with additional neuroprotective properties[15]. Phase II clinical trial to evaluate the safety and efficacy of a brimonidine tartrate intravitreal implant (Brimo DDS, Allergan)in patients with dry AMD showed that Brimo DDS reduced the rate of progression at 1 year.[16]

3. Minocycline is a tetracycline derivative with neuro protective properties. Presently, there are ongoing phase II trials that are evaluating the effects of oral minocycline (100 mg, twice daily) and doxycycline (40 mg, daily) in the treatment of AMD patients with geographic atrophy.[17, 18]

4. Anti Inflammatory agents:

a. CLG561 is an inhibitor of properdin. It acts by destabilizing the alternative pathway. A phase 2 study of 114 participants evaluated the safety and efficacy of 12 (every 28 days) intravitreal injections of CLG561 as a monotherapy and in combination with LFG316(Tesidolumab) which is a complement factor C5 inhibitor as compared to sham in subjects with GA [19]. Results have yet to be published.

b. APL-2 is a synthetic cyclic peptide that binds specifically to C3, effectively blocking all three pathways of complement activation: classical, lectin, and alternative. DERBY and OAKS studies compared efficacy and safety of APL-2 (15 mg/0.1 ml) intravitreal injection monthly or once every other month for 24 month with sham injections. The primary endpoint was change in total area of GA from baseline measured by FAF. Results are still awaited.[19]

c. Zimura (Ophthotech) completed patient recruitment for its phase 2b clinical trial of Zimura (avacincaptad pegol), a complement factor C5 inhibitor. A total of 286 patients have been enrolled into this randomized, double-masked, sham controlled multicenter clinical trial. This clinical trial is designed to assess the safety and efficacy of various Zimura dosing regimens over 12 months. Results are awaited.[19]

5. Anti-oxidative stress agents: Risuteganib (ALG-1001) is an integrin inhibitor and thus down regulates oxidative stress response and restores retinal homeostasis. Currently, a phase 2 clinical trial designed to evaluate the safety and efficacy of Risuteganib (1.0 mg) in patients with intermediate non-exudative AMD is underway.[20]

6. Amyloid Beta Targets (MRZ-99030) : Amyloid protein has been identified as a primary component of drusen in patients with AMD. Amyloid Beta Targets is an Aβ aggregation modulator, previously reported to prevent the formation of soluble toxic oligomeric Aβ species. Amyloid beta target is a dipeptide administered as intravenous injection. It promotes the formation of large, amorphous/globular Ab species when present at a 10:1 stoichiometric excess to Ab. Phase one studies have been completed involving this agent.[21]

7. Visual cycle modifying agents:ALK-001 modulates vitamin A metabolism, by decreasing toxic vitamin A aggregates. Phase 2 Study of ALK-001 in Geographic Atrophy (SAGA) is still going on. One of the earliest changes in the retina that precede symptoms of AMD is the formation of toxic vitamin A dimers. Replacing the retina's vitamin A with ALK-001 slows the formation of toxic vitamin A dimers. To date, ALK-001 is the only small molecule designed to prevent the dimerization of vitamin A that has demonstrated functional preservation of visual function in animal models. The central hypothesis of this work is that retarding vitamin A dimerization will slow the development and/or progression of AMD.[22]

8. Choroidal blood flow enhancing agents: Alprostadil is a naturally occuring Prostaglandin E1.Phase 3 study proved that Alprostadil infusion was superior to placebo treatment in patients affected by dry AMD. Patients treated with Alprostadil showed a BCVA greater than 0.94 lines compared with patients treated by placebo after 3 months, increasing to 1.51 lines at 6-month follow-up.[23]

9. Newer Anti VEGF agents

a. Conbercept consists of the VEFG binding domains of human VEGFR-1 and VEGFR-2 combined with the Fc portion of the human immunoglobulin G. It binds VEGF A,VEGF B and Placental growth factor[24]. Hundred and twenty two patients with exudative AMD were randomized 1:1 to receive either 0.5 mg or 2.0 mg conbercept for 3 consecutive monthly doses. After the third dose, subjects were again randomized to either monthly or as-needed (PRN) therapy, without changing the dose of conbercept that they were receiving. At the third month, mean BCVA improvement was there in both the groups.

b. Faricimabis the first bispecific antibody to simultaneously bind and neutralise both angiopoietin-2 and VEGF-A. In nAMD, Ang-2 works synergistically with VEGF to drive pathologic blood vessel permeability and destabilisation. STAIRWAY is a phase II, multicentre, RCT, investigating the efficacy, safety and pharmacokinetics of faricimab administered with extended dosing regimens in 76 treatment-naive patients with nAMD.[25]

c. Brolucizumab is a humanized, single-chain antibody fragment inhibitor of VEGF-A.It inhibits all isoforms of VEGF-A including VEGF 165.Phase III of the HAWKstudy involved990 patientsover2-year to compare the efficacy and safety of Brolucizumab 3mg and 6 mg vs. Aflibercept 2 mg in subjects with nAMD. Results show noninferiority of Brolucizumabin BCVA vs aflibercept. More patients demonstrated sustained dryness for ≥2 and ≥3 consecutive visits. Superior anatomic results were seen for brolucizumab at Weeks 16 and 48. Overall ocular and nonocular adverse event rates for brolucizumab were comparable to aflibercept(26). HARRIER study, a phase IIIdouble-masked, multi-center, two-arm study comparing the efficacy and safety of brolucizumab vs. aflibercept in 660 subjects with nAMDover 2years. The study showed noninferiority as a majority of patients maintained BCVA on q12w intervaland superior anatomic results for brolucizumab at weeks 16 and 48.[26]

d. OPT-302is a soluble form of VEGF receptor 3 comprising the extracellular domains 1-3 of human VEGF receptor 3 and the Fc fragment of human IgG1. The VEGFR-3 or "trap" molecule blocks the activity of the proteins VEGF-C and VEGF-D.OPT-302 is used in combination with inhibitors of VEGF-A. Combination therapy of OPT-302 and a VEGF-A inhibitor achieves more complete blockade of members of the VEGF family. Phase 2 clinical trial enrolled 366 treatment-naive wet AMD patients who were randomized in a 1:1:1 ratio to receive one of the following treatment regimens administered every 4 weeks for 24 weeks: OPT-302 (0.5 mg) in combination with ranibizumab (0.5 mg); OPT-302 (2.0 mg) in combination with ranibizumab (0.5 mg); or sham in combination with ranibizumab (0.5 mg).Superior visual gains were noted in the combination therapy.[27]

Diabetic Macular Edema:

While there is no doubt that anti–VEGF-A monotherapy has revolutionized the treatment of diabetic macular edema (DME), there still remains a subset of patients who are non-responders. The unmet need presented by these patient forms the impetus for developingnew options for the treatment of DME. We enumerate a few that show promise

1. Next-generation anti–VEGF-A drugs

a. Conbercept is a recombinant human VEGF receptor-Fc fusion protein, which inhibits VEGF-A, VEGF-B, and placental growth factor (PlGF).The FRONTIER and SAILING studies showed improvement in visual acuity and concomitant decreases in retinal thickness on OCT in patients with DME.[28]

b. Abicipar Pegol belongs to the class of genetically engineered antibodymimetic proteins called designed ankyrin repeat proteins (DARPins). Results from the phase 2 PALM study showed that abicipar pegol, injected every 8 or12 weeks in patients with DME, offered functional and anatomic effects similarto those of ranibizumab injected monthly.[29]

2. Suprachoroidal corticosteroid: The injection of triamcinolone acetonide (CLS-TA; Clearside Biomedical) into the suprachoroidal space is a novel approach to the treatment of patients with DME.The HULK clinical trial examined suprachoroidal CLS-TAwith and without intravitreal aflibercept and showed signs of increased efficacyand durability with the investigational drug.[30]

References :

1. Witmer MT, Parlitsis G, Patel S, Kiss S. Comparison of ultra-widefield fluorescein angiography with the Heidelberg Spectralis® noncontact ultra-widefield module versus the Optos® Optomap®. Clin Ophthalmol. 2013;7:389–94.
2. Patel RD, Messner L V, Teitelbaum B, Michel KA, Hariprasad SM. Characterization of ischemic index using ultra-widefield fluorescein angiography in patients with focal and diffuse recalcitrant diabetic macular edema. Am J Ophthalmol. 2013;155(6).
3. Dai S, Chow K, Vincent A. Efficacy of wide-field digital retinal imaging for retinopathy of prematurity screening. Clin Exp Ophthalmol. 2011;39(1):23–9.
4. Tan ACS, Fleckenstein M, Schmitz-Valckenberg S, Holz FG. Clinical Application of Multicolor Imaging Technology. Ophthalmologica. Karger Publishers; 2016;236(1):8–18.
5. Povazzay B, Hermann B, Hofer B, Kaji V, Simpson E, Bridgford T, et al. Wide-field optical coherence tomography of the choroid in vivo. Investig Ophthalmol Vis Sci. 2009;50(4):1856–63.
6. Mori K, Kanno J, Gehlbach PL. Retinochoroidal morphology described by wide-field montage imaging of spectral domain optical coherence tomography. Retina. 2016;36(2):375–84.
7. McNabb RP, Grewal DS, Mehta R, Schuman SG, Izatt JA, Mahmoud TH, et al. Wide field of view swept-source optical coherence tomography for peripheral retinal disease. British Journal of Ophthalmology. 2016;
8. Vinekar A, Mangalesh S, Jayadev C, Maldonado RS, Bauer N, Toth CA. Retinal Imaging of Infants on Spectral Domain Optical Coherence Tomography. Biomed Res Int. Hindawi; 2015 Jul 6;2015:782420.
9. Pircher M, Zawadzki RJ. Review of adaptive optics OCT (AO-OCT): principles and applications for retinal imaging [Invited]. Biomed Opt Express. Optical Society of America; 2017 May 1;8(5):2536.
10. Song H, Rossi EA, Latchney L, Bessette A, Stone E, Hunter JJ, et al. Cone and rod loss in stargardt disease revealed by adaptive optics scanning light ophthalmoscopy. JAMA Ophthalmol. 2015;133(10):1198–203.
11. Jacob J, Krivosic V, Paques M, Tadayoni R, Gaudric A. Cone density loss on adaptive optics in early macular telangiectasia type 2. Retina. 2016;36(3):545–51.

12. Choi WJ, Mohler KJ, Potsaid B, Lu CD, Liu JJ, Jayaraman V, et al. Choriocapillaris and choroidal microvasculature imaging with ultrahigh speed OCT angiography. PLoS One. 2013;8(12).

13. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). Int J Retin Vitr. BioMed Central; 2015 Apr 15;1(1):5.

14. Merry GF, Munk MR, Dotson RS, Walker MG, Devenyi RG. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration. Acta Ophthalmol. 2017;95(4):e270–7.

15. Doozandeh A, Yazdani S. Neuroprotection in glaucoma. Journal of Ophthalmic and Vision Research. 2016. p. 209–20.

16. Kuppermann BD et al. Brimonidine drug delivery system generation 1 in patients with geographic atrophy: Post hoc analysis of a phase 2 study [Internet]. [cited 2018 Apr 5]. Available from: https://www.healio.com/ophthalmology/retina-vitreous/news/online/%7B7e23cf82-d686-4125-ac42-0f6c610dc44b%7D/intravitreal-implant-with-brimonidine-reduced-ga-lesion-growth-in-phase-2-study

17. Evaluation of Oral Minocycline in the Treatment of Geographic Atrophy Associated With Age-Related Macular Degeneration - Full Text View - ClinicalTrials.gov [Internet]. [cited 2018 Apr 5]. Available from: https://clinicaltrials.gov/ct2/show/NCT02564978

18. Yates Paul. Clinical Study to Evaluate Treatment With ORACEA® for Geographic Atrophy (TOGA) - Full Text View - ClinicalTrials.gov [Internet]. [cited 2018 Apr 5]. Available from: https://clinicaltrials.gov/ct2/show/NCT01782989

19. Enoch Kassa, Thomas A Ciulla, Rehan M Hussain & Pravin U Dugel (2019):Complement inhibition as a therapeutic strategy in retinal disorders, Expert Opinion on BiologicalTherapy, DOI: 10.1080/14712598.2019.1575358

20 Kaiser, P.K.; Boyer, D.S.; Campochiaro, P.A.; Heier, J.; Kornfield, J.; Kuppermann, B.D.; Quiroz-Mercado, H.;Karageozian, L.; Kutscher, L.; Karpus, M.; et al. Topline results from a prospective, double-masked,placebo-controlled phase-2b clinical study evaluating ALG-1001 (Luminate) in patients with diabetic macular edema. Invest. Ophthalmol. Vis. Sci. 2017, 58, 2029.

21 Parsons, C.G., et al., MRZ-99030 e A novel modulator of Ab aggregation: I e Mechanism of action (MoA) underlying the potential neuroprotective treatment of Alzheimer's disease, glaucoma and age-related macular degeneration (AMD), Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2014.12.038

22 A Phase 2a clinical trial of ALK-001 in geographic atrophySaad, Leonide Washington, Ilyas Alkeus Pharmaceuticals, Inc., Cambridge, MA, United States

23 Augustin, Albert J., Curt Diehm, Frank Grieger and Jürgen W G Bentz. "Alprostadil infusion in patients with dry age related macular degeneration: a randomized controlled clinical trial." Expert opinion on investigational drugs 22 7 (2013): 803-12 .

24 Li X. Xu G, Wang Y, et al. AURORA study group. Safety and efficacy of conbercept in neovascular age-related macular degeneration: results from a 12-month randomized phase 2 study: AURORA study. Ophthalmology. 2014;121(9):1740-1747

25 Khanani AM, et al. Simultaneous Inhibition of VEGF and Ang-2 with Faricimab in Neovascular AMD: STAIRWAY Phase 2 Results. Presented at the 2018 American Academy of Ophthalmologists (AAO) Annual Meeting; 2018 Oct 26; Chicago, United States.

26 Dugel PU, Koh A, Ogura Y, Jaffe GJ, Schmidt-Erfurth U, Brown DM, et al. HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration [Internet]. Ophthalmology. Elsevier; 2019 [cited 2019Nov30]. Available from: https://www.sciencedirect.com/science/article/pii/S0161642018330185

27 Anti-Vascular Endothelial Growth Factor Use and Atrophy in AMD[Internet]. [cited 2019Nov30]. Available from: https://www.sciencedirect.com/science/article/pii/S0161642019322821

28 Safety and efficacy by multiple injection of KH902 in patients with diabetic macular edema (DME) (Frontier-1). https://clinicaltrials.gov/ct2/show/NCT01324869.

29. Hassan TS. A multicenter, double masked phase 2 clinical trial evaluating abicipar pegol for diabetic macular edema. Paper presented at: American Academy of Ophthalmology Annual Meeting; October 14-18, 2016; Chicago, IL.

30 Wykoff CC. Suprachoroidal triamcinolone acetonide with and without intravitreal aflibercept for diabetic macular edema: Phase 1/2 HULK study. Paper presented at American Academy of Ophthalmology Retina Subspecialty Day; November 10-11, 2017; New Orleans.

JOURNAL UPDATE

Repeat SLT can Provide Drop-free IOP Control for 18 Months

According to this post hoc analysis, repeat selective laser trabeculoplasty (SLT) offers effective IOP control in glaucomatous eyes requiring retreatment. The study included 115 treatment-naïve eyes with open-angle glaucoma or ocular hypertension undergoing 360° SLT twice within 18 months. Two months after the repeat procedure, participants showed a greater adjusted absolute IOP reduction than from the initial procedure. Approximately 67% of study eyes maintained drop-free IOP at 18 months, with no adverse events. Ophthalmology, April 2020