خبرنامه انجمن فوق تخصصی ویتره و رتین

دی ماه ۱۳۹۳ – سال دوم – شماره هفتم

Genetic testing before recommending AREDS?

The January issue of Ophthalmology tackles the ongoing debate over the value of genotyping patients with wet AMD before recommending AREDS supplementation. Aneditorial considers whether clinicians should follow the recommendations of Dr. Carl Awh and test patients to determine what supplements they should take or whether to follow the guidance of Dr. Emily Chew and recommend AREDS supplements without engaging in genetic testing.

Ophthalmology, January 2015

Neovascularization subtype linked to increased geographic atrophy risk

This retrospective review evaluated factors associated with the growth of geographic atrophy in a consecutive series of 94 eyes with treatment-naive neovascular AMD. Subjects received anti-VEGF therapy on a treat-and-extend regimen. Using both SD-OCT and fluorescein angiography, clinicians graded the lesions at baseline as 1 of 4 types: subretinal pigment epithelium, subretinal, intraretinal, or mixed neovascularization. The odds of developing apparent geographic atrophy were significantly lower in patients with subretinal pigment epithelium compared with the other lesion types ($P < 0.001$).

Retina, February 2015

Smartphone app measures visual acuity for diabetic retinopathy screening

February 12, 2015

A smartphone application with functional and imaging capabilities can be comparable to an in-office examination when measuring visual acuity for diabetic retinopathy screening, Mark S. Blumenkranz, MD, told colleagues at Angiogenesis, Exudation, and Degeneration 2015.

“It’s another example of mobile out-of-office monitoring technology that can be combined with a fully integrated EHR to provide a window into disease activity and management,” Blumenkranz said.

A specialized plastic 3-D adapter records still images or video that downloads automatically to a website from any location with wireless capabilities.

In a prospective nonrandomized consecutive trial, 100 eyes of 50 patients were examined. Each patient underwent a standard clinical ophthalmic exam, including dilation, in addition to a near corrected visual acuity examination using the smartphone app by a different examiner. Visual

acuity, grade of iris neovascularization, grade of diabetic retinopathy, and masked grading and interobserver adjudication were compared.

A high degree of correlation was found between the use of the smartphone app and an in-office examination to determine visual acuity, showing the same mean and median outcomes.

“It has demonstrated ability to document disease, to determine who needs to be and does not need to be treated,” Blumenkranz said. “Therefore, it may have a useful role in remote screening for diabetic eye disease, particularly for triaging which patients in high-risk groups need treatment, or patients who may not be remote but have limited access to care due to demographic and socioeconomic factors.” – by Kristie L. Kahl and Patricia Nale, ELS

Anti-PDGF, anti-VEGF combination for neovascular AMD well tolerated

An anti-PDGF agent combined with an anti-VEGF was well-tolerated by patients with neovascular age-related macular degeneration, according to results of a phase 1 clinical trial. “The phase 1 study did not reveal any treatment-emergent adverse events and no reports of inflammation,” Jeffrey S. Heier, MD, said at Angiogenesis, Exudation, and Degeneration 2015. “The treatments were well-tolerated.”

Ongoing study focuses on REGN2176-3 (Regeneron), an anti-PDGF receptor-beta monoclonal antibody co-formulated with 2 mg Eylea (aflibercept,Regeneron) as a single 50-µL intravitreal injection.

PDGF, a growth factor involved in the regulation of cell growth and division, plays a major role in blood vessel formation and maturation, Heier said.

The phase 1 open-label study included four cohorts of three patients who received REGN2176-3 combined with aflibercept at baseline and at 4 weeks.

Mean baseline best corrected visual acuity was 63 letters, and mean baseline central retinal thickness was 312 µm (range: 198 µm to 454 µm).

Combined anti-PDGF/anti-VEGF dosage ratios were 0.2 mg:2 mg in the first cohort, 0.5 mg:2 mg in the second cohort, 1 mg:2 mg in the third cohort and 3 mg:2 mg in the fourth cohort.

Study results showed no dose-limiting toxicities, intraocular inflammation or treatment-related serious adverse events.

Visual acuity was stable or increased in a majority of patients.

Central retinal thickness decreased in all four cohorts, with the greatest decrease in the first and second cohorts, “but keep in mind cohorts one and two had the large majority of treatment-naïve patients,” Heier said.

A phase 2 clinical trial scheduled to begin in the first quarter will include 500 patients randomized to receive high-dose or low-dose REGN2176-3 combined with aflibercept. A control group will receive aflibercept 2 mg alone.

Telemedicine identifies need for ROP referrals

Non-physician image readers correctly identified 90% of infants with referral warranted ROP.

Ocular Surgery News U.S. Edition, February 10, 2015

Training non-physicians to remotely obtain and grade images to detect potentially serious retinopathy of prematurity reliably identifies patients needing referral, according to a study.

In a study published in JAMA Ophthalmology, researchers evaluated the effectiveness of a telemedicine system to detect referral-warranted ROP — that is, those that need an examination by an ophthalmologist — by comparing digital images obtained and graded by trained non-physicians with the same cases graded by ophthalmoscopic examination.

This study disclosed that "The non-physician readers correctly identified 90% of infants with referral-warranted ROP, meaning that we identified 90% of the infants on a single visit who had potential serious disease and who should be evaluated for possible treatment".

Study: Telemedicine screening for proliferative diabetic retinopathy makes economic sense

In a simulation, screening saved $36 per patient vs. no screening.

Ocular Surgery News U.S. Edition, February 10, 2015

Compared with no screening, telemedicine screening for proliferative diabetic retinopathy in an urban primary care office saved $36 per patient over the long term, according to an economic simulation study. "Our current rates of compliance with diabetic retinopathy screening guidelines are poor nationwide," lead investigator Christopher J. Brady, MD, said. "Telemedicine is a potential means for increasing our rates of screening compliance. Assuming all of the medical barriers can be overcome, cost is a chief remaining barrier." "Our current rates of compliance with diabetic retinopathy screening guidelines are poor nationwide," lead investigator Christopher J. Brady, MD, said. "Telemedicine is a potential means for increasing our rates of screening compliance. Assuming all of the medical barriers can be overcome, cost is a chief remaining barrier."

A Monte Carlo simulation found that screening for proliferative diabetic retinopathy saved even more money, a median of $48 per person, due to a sophisticated computer algorithm that took

into account more variables, such as a 1% or 2% rate of disease, or a laser charge of $900 vs. $1,200.

Treat-and-extend AMD regimen sustains outcomes for up to 3 years

Am J Ophthalmol. 2014;doi:10.1016/j.ajo.2014.09.011.

A treat-and-extend protocol improved vision and reduced retinal thickness for up to 3 years in patients with neovascular age-related macular degeneration, according to study findings. The retrospective study included 212 eyes of 189 patients with treatment-naïve neovascular AMD treated with Lucentis 0.5 mg/0.05 mL (ranibizumab,Genentech) or Avastin 1.25 mg/0.05 mL (bevacizumab, Genentech) for at least 1 year under a treat-and-extend regimen.

RELATE study: Increased ranibizumab, laser yield minimal benefits

Ocular Surgery News U.S. Edition, February 10, 2015

BOSTON — An increased dose of ranibizumab (2mg vs 0.5mg) offered no added benefit in eyes with retinal vein occlusion, according to a study presented here. Additionally, laser photocoagulation did not improve vision or reduce edema significantly more than ranibizumab, Peter A. Campochiaro, MD, said at Macula 2015.

FDA Approves Lucentis For Treatment Of Diabetic Retinopathy In People With DME. Genentech recently announced that the FDA approved Lucentis (ranibizumab injection) for the treatment of diabetic retinopathy in people with diabetic macular edema. The agency granted Lucentis Breakthrough Therapy Designation and Priority Review for this indication based on results from the two identically designed, parallel, double-masked, sham treatment-controlled RISE and RIDE Phase III clinical trials.

Monitoring Wet AMD Using OCT

Traditionally, fundus fluorescein angiography has been considered the reference standard to detect wet age-related macular degeneration activity, but FFA is costly and invasive. Replacement of FFA by optical coherence tomography can be justified if there is a substantial agreement between tests. This systematic review and meta-analysis compared the accuracy of OCT with alternative tests for monitoring wet AMD and detecting disease activity among eyes previously treated for this condition. This study demonstrated that there is substantial disagreement between OCT and FFA findings in detecting active disease in patients with wet

AMD who are being monitored. Both methods may be needed to monitor patients comprehensively with wet AMD.

SOURCE: Castillo MM, Mowatt G, Elders A, et al. Optical coherence tomography for the monitoring of neovascular age-related macular degeneration: a systematic review. Ophthalmology. 2015;122(2):399–406.

Stereotactic Radiotherapy for Wet AMD

In this randomized, double-masked, sham-controlled, multicenter clinical trial, investigators sought to determine the safety and efficacy of low-voltage, external-beam, stereotactic radiotherapy (SRT) for patients with wet age-related macular degeneration. The authors concluded that a single dose of SRT significantly reduces intravitreal injections over two years, the investigators concluded. Radiation can induce microvascular change, but in only 1% of eyes does this possibly affect vision. The best response occurs when AMD lesions fit within the treatment zone and they are actively leaking.

Source: Jackson TL, Chakravarthy U, Slakter JS, et al; on behalf of the INTREPID Study Group. Stereotactic radiotherapy for neovascular age-related macular degeneration: year 2 results of the INTREPID Study. Ophthalmology. 2015;122(1):138–145.

Development of Vision-Threatening Lesions With Longer-Term Follow-Up After Treatment of Wet AMD

This study was designed to assess the development of vision-threatening lesions after initiating anti-vascular endothelial growth factor for choroidal neovascularization in eyes with age-related macular degeneration. The authors concluded that longer-term follow-up of wet AMD managed with anti-VEGF therapy suggests that predominantly hemorrhagic lesions may develop within 3.5 years of initiating therapy and more than 3.5 years after initiating therapy. In contrast, new areas of GA beyond the boundaries of the CNV lesion as defined at initiation of anti-VEGF therapy seem unlikely to develop if there is no GA outside of the CNV lesion initially.

Source: Tanaka E, Chaikitmongkol V, Bressler SB, Bressler NM. Vision-threatening lesions developing with longer-term follow-up after treatment of neovascular age-related macular degeneration. Ophthalmology. 2015;122(1):153–161.

Impact of Switching Intravitreal Anti-VEGF Treatment in Wet AMD

This retrospective review of patients with wet age-related macular degeneration with first treatment using intravitreal bevacizumab (Group One) or ranibizumab (Group Two) compared the outcomes after switching to the other drug due to poor treatment effect. Results of this study showed that mean BCVA decreased over time in both groups; however, nearly 30% of the eyes in each group showed vision improvement after switching. Mean CRT decreased in both groups, which was more pronounced after being switched from bevacizumab to ranibizumab. In wet AMD, a switch between ranibizumab and bevacizumab can be considered as a further therapy option if poor treatment effect is seen with the initial therapy.

Source: Küçükerdünmez C, Gelisken F, Yoeruek E, et al. Switching intravitreal anti-VEGF treatment in neovascular age-related macular degeneration. Eur J Ophthalmol. 2015;25(1):51–56.

Microperimetry of Nascent GA in AMD

To determine the microperimetric retinal sensitivity in areas with nascent geographic atrophy compared with other pathological features in eyes with intermediate age-related macular degeneration, scientists conducted this prospective study in which participants with bilateral intermediate AMD underwent microperimetry examinations and high-resolution spectral-domain optical coherence tomography scans. This study demonstrated that areas of nascent GA were characterized by worse microperimetric retinal sensitivity compared with nonatrophic areas in eyes with intermediate AMD, but better retinal sensitivity compared with areas of drusen-associated atrophy detected on SD-OCT. Furthermore, areas of nascent GA were also not always the worst performing point in an eye. These findings further our understanding of the functional changes occurring in novel SD-OCT identified pathological changes in intermediate AMD.

Source: Wu Z, Ayton LN, Luu CD, Guymer RH. Microperimetry of nascent geographic atrophy in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2015;56(1):115–121.

Baseline Choroidal Thickness as a Predictor for Response to Anti-VEGF Therapy in DME

In this retrospective, consecutive case series, researchers sought to determine the association between baseline subfoveal choroidal thickness and short-term response to intravitreal anti-vascular endothelial growth factor therapy in diabetic macular edema. Findings of this study

showed that baseline subfoveal choroidal thickness may help predict which patients with DME will respond more favorably in the short term to intravitreal anti-VEGF pharmacotherapy. In this study, eyes with a thicker baseline subfoveal choroidal thickness had better short-term anatomic and functional responses.

Source: Rayess N, Rahimy E, Ying G, et al. Baseline choroidal thickness as a predictor for response to anti-vascular endothelial growth factor therapy in diabetic macular edema. Am J Ophthalmol. 2015;159(1):85–91.

Verteporfin Dose Comparison for Treatment of Acute CSC

A randomized clinical trial is needed to evaluate what is the best photodynamic therapy protocol to use for acute central serous chorioretinopathy. To compare the efficacy and safety of a 50%-dose of verteporfin (a method of PDT) with the efficacy and safety of a 30%-dose for acute CSC, Chinese investigators conducted this multicenter, noninferiority, double-masked, randomized, controlled, clinical trial. The study investigators concluded that a 50% dose of verteporfin may be more effective at resolving subretinal fluid and fluorescein leakage, and with better visual outcomes, than a 30% dose for acute CSC.

Source: Zhao M, Zhang F, Chen Y, et al. A 50% vs. 30% dose of verteporfin (photodynamic therapy) for acute central serous chorioretinopathy: one-year results of a randomized clinical trial. Am J Ophthalmol. 2015;Jan 2. [Epub ahead of print]. DOI: 10.1001/jamaophthalmol.2014.5312.

Phase II Clinical Trial for the Treatment of Macular Edema Associated With Noninfectious Uveitis Initiated

In a recent press release, Clearside Biomedical Inc. announced the enrollment of the first patient in a Phase II randomized, controlled, masked, multicenter clinical trial for the treatment of macular edema associated with noninfectious uveitis using the company's proprietary formulation of triamcinolone acetonide, CLS-TA, administered via suprachoroidal injection using its proprietary microinjector. Roughly 30 patients will be randomized 1:1 to receive either a single 4.0-mg dose or a single lower dose of 0.8 mg of CLS-TA. The trial is designed to explore safety and efficacy information on SCS injection of each of these doses of CLS-TA. According to Clearside, the primary efficacy endpoint of the trial will be the mean change from baseline in retinal thickness at two months after treatment. Secondary efficacy endpoints will include visual acuity improvements at one and two months post-treatment, measured by the mean change in best-corrected visual acuity from baseline. Safety measures will be monitored over the two-month observation period and will include the incidence of adverse events and serious adverse events, including increases in intraocular pressure.

Source: Clearside Biomedical Inc., January 2015.

Carl Zeiss Meditec Invests in Oraya's Innovative Wet AMD Solution

Oraya Therapeutics Inc. has developed and commercialized a low-energy X-ray radiation therapy (the “Oraya Therapy”) for the treatment of wet age-related macular degeneration, currently available in Germany, the UK and Switzerland. Carl Zeiss Meditec says the collaboration is intended to accelerate and expand these initial European market developments. Specific terms of the agreement were not disclosed, but Carl Zeiss Meditec will be making a meaningful strategic investment in Oraya and further opportunities to leverage the companies' respective technical and market expertise and resources will be reviewed. Find out more here.

Source: Carl Zeiss Meditec, January 2015.

Impact of Reduced-Fluence PDT for Chronic CSC on Regional Choroid Thickness

This prospective, consecutive, interventional case series evaluated macular choroidal thickness following reduced-fluence photodynamic therapy for chronic central serous chorioretinopathy.

This study showed that chronic CSC eyes showed significantly thicker choroids in the macular area. After reduced-fluence PDT, macular choroidal thickness became thinner within six months of treatment.

SOURCE: Manabe S, Shiragami C, Hirooka K, et al. Change of regional choroid thickness after reduced-fluence photodynamic therapy for chronic central serous chorioretinopathy. Am J Ophthalmol. 2015; Jan 29.

Intravenous Secukinumab in Noninfectious Uveitis Requiring Steroid-Sparing Immunosuppressive Therapy

Secukinumab, a fully human anti-interleukin-17A monoclonal antibody, exhibited promising activity in a proof-of-concept study when administered in intravenous doses to patients with active, chronic, noninfectious uveitis. The authors of this multicenter, randomized, double-masked, dose-ranging, Phase II clinical trial compared the efficacy and safety of different IV and subcutaneous (SC) doses of secukinumab in patients with noninfectious uveitis. This study disclosed that intravenous secukinumab was effective and well-tolerated in noninfectious uveitis requiring systemic corticosteroid-sparing immunosuppressive therapy. Greater activity with IV dosing suggests that patients may not receive sufficient drug with SC administration. High-dose IV secukinumab may be necessary to deliver secukinumab in therapeutic concentrations.

Source: Letko E, Yeh S, Foster CS, et al; for the AIN457A2208 Study Group. Efficacy and safety of intravenous secukinumab in noninfectious uveitis requiring steroid-sparing immunosuppressive therapy. Ophthalmology. 2015; Jan 29.

Efficacy and Safety of Intravitreal Bevacizumab vs. Ranibizumab in the Treatment of Macular Edema Due to BRVO

Researchers in India sought to assess the efficacy and safety of intravitreal bevacizumab (IVB) compared with ranibizumab (IVR) in the treatment of macular edema due to branch retinal vein occlusion in this prospective, randomized, non-inferiority trial. This study demonstrated significant gain in visual acuity in eyes with BRVO treated with either bevacizumab or ranibizumab. Pro re nata strategy was effective in maintaining the visual gain.

Source: Narayanan R, Panchal B, Das T, et al.; on behalf of the MARVEL study group. A randomised, double-masked, controlled study of the efficacy and safety of intravitreal bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion: MARVEL Report No. 1. Br J Ophthalmol. Jan 28.

Outer Retinal Tubulation in the Comparison of Age-Related Macular Degeneration Treatments Trial

The authors of this prospective cohort study within a randomized clinical trial sought to determine the prevalence of, risk factors for, and visual acuity correlations with outer retinal tubulation seen on spectral-domain optical coherence tomography in eyes with wet age-related macular degeneration after anti-vascular endothelial growth factor therapy.

At two years after initiation of anti-VEGF therapy for neovascular AMD, ORTs are present in a substantial proportion of eyes. The authors identified baseline features that independently predict ORTs. It is important to identify ORTs because eyes with ORTs have worse VA outcomes than those without this finding.

Source: Lee JY, Folgar FA, Maguire MG, et al; for the CATT Research Group. Outer retinal tubulation in the Comparison of Age-Related Macular Degeneration Treatment Trails (CATT). Ophthalmology. 2014;121(12):2423–2431.

Relationship Between Retinal Sensitivity Assessed by Microperimetry and Contrast Sensitivity in DME

Investigators in Korea sought to examine the relationship between contrast sensitivity and retinal sensitivity assessed by microperimetry (MP) in diabetic retinopathy with clinically significant macular edema. This study showed that contrast sensitivity and retinal sensitivity showed moderately significant correlations in CSME. However, neither was correlated with retinal thickness in patients with CSME. It could be that contrast sensitivity and microperimetry are complementary to each other and are useful tools in the evaluation of functional vision.

Source: Kim YH, Yun C, Kim JT, et al. The correlation between retinal sensitivity assessed by microperimetry and contrast sensitivity in diabetic macular oedema. Br J Ophthalmol. 2014;98(12):1618–1624.

Comparison of Monthly vs. As-Needed Ranibizumab Injections in Patients With RVO

This 15-month, randomized, open-label, vision-examiner masked study compared p.r.n. and monthly injections of 0.5 mg ranibizumab in retinal vein occlusion patients stabilized by monthly injections. It was discovered that after edema resolution from seven or more monthly ranibizumab injections in RVO subjects, visual outcomes at month 15 were excellent and not significantly different in subjects treated p.r.n. versus those who continued monthly injections.

Source: Campochiaro PA, Wykoff CC, Singer M, et al. Monthly versus as-needed ranibizumab injections in patients with retinal vein occlusion. Ophthalmology. 2104;121(12):2432–2442.

SciFluor Life Sciences Awarded U.S. Patent for Topical Treatment of Retinal Disease

SciFluor Life Sciences LLC recently announced that the U.S. Patent and Trademark Office (USPTO) has issued U.S. Patent No. 8,901,144 with claims covering the novel compound SF0166. SF0166 is a small-molecule integrin antagonist designed to treat retinal disease, including age-related macular degeneration and diabetic macular edema via topical administration to the eye.

Source: SciFluor Life Sciences LLC, December 2014.

Eidon Retinal Imaging System Cleared for Sale in the United States

CenterVue has received FDA clearance for its Eidon true-color confocal scanner, a fully automated retinal imaging system that combines the advantages of confocal scanning with true-color imaging capabilities. CenterVue says its white-light, confocal imaging technology facilitates diagnosis and management of retinal disease and that the combination of confocal imaging and white light illumination provides greater contrast and superior image quality over a traditional fundus camera. Additionally, Eidon streamlines image acquisition and ensures minimum operator involvement by automatically aligning the patient's pupil, focusing on the retina and capturing images using a soft light source.

Source: CenterVue Inc., December 2014.

Eylea Injection Accepted for Priority Review for Diabetic Retinopathy in Patients with DME

According to Regeneron Pharmaceuticals Inc., the FDA has accepted for priority review the supplemental biologics license application for Eylea (aflibercept) Injection for the treatment of diabetic retinopathy in patients with diabetic macular edema. Under the Prescription Drug User Fee Act, the goal for a priority review is six months, for a target action date of March 30, 2015. Visit www.regeneron.com to find out more.

Source: Regeneron Pharmaceuticals Inc., December 2014.

FDA OKs Lucentis for Diabetic Retinopathy in DME Patients

The US Food and Drug Administration (FDA) has expanded the approved use for Lucentis (ranibizumab injection 0.3 mg, Genentech, Inc, South San Francisco, CA) to treat diabetic retinopathy in patients with diabetic macular edema (DME).

“Diabetes is a serious public health crisis, affecting more patients every year,” said Edward Cox, MD, MPH, director of the Office of Antimicrobial Products in the FDA’s Center for Drug Evaluation and Research. “[This] approval gives patients with diabetic retinopathy and diabetic macular edema the first significant therapy to treat this vision-impairing complication.”

The FDA reports that the safety and efficacy of Lucentis to treat diabetic retinopathy with DME were established in 2 clinical studies involving 759 participants treated and followed for 3 years. In the 2 studies, participants treated with Lucentis showed significant improvement in the severity of their diabetic retinopathy at 2 years compared with patients who did not receive an injection.

According to the FDA, the most common side effects include bleeding of the conjunctiva, eye pain, floaters, and increased intraocular pressure. Serious side effects include endophthalmitis and retinal detachments.

The FDA granted Lucentis for diabetic retinopathy with DME breakthrough therapy designation. According to the FDA, the agency can designate a drug a breakthrough therapy at the request of the sponsor if preliminary clinical evidence indicates the drug may demonstrate a substantial improvement over available therapies for patients with serious or life-threatening conditions.

The FDA reports that it also reviewed the new use for Lucentis under the agency’s priority review program, which provides for an expedited review of drugs that demonstrate the potential to be a significant improvement in safety or effectiveness in the treatment of a serious condition.

Previously, the FDA approved Lucentis to treat DME and macular edema secondary to retinal vein occlusions. Lucentis also is approved to treat neovascular AMD.

Updated February 6, 2015

Health Canada Approves Argus II Retinal Prosthesis

Second Sight Medical Products, Inc. (Sylmar, CA) has announced that the Argus II Retinal Prosthesis System has been approved by Health Canada to treat individuals suffering from severe to profound outer retinal degeneration.

The Argus II is the first artificial retina in the world approved by the US Food and Drug Administration (FDA), Health Canada, and Europe (CE Mark). This device has been implanted in more than 100 individuals worldwide. An estimated 13,000 people in Canada and 1.2 million worldwide have outer retinal degeneration due to retinitis pigmentosa.

According to Second Sight, the Argus II system induces visual perception in blind individuals by stimulating the retina's remaining cells with electrical impulses; this results in a perception of light patterns in the brain.

Updated January 13, 2015

New Research Shows Potential Benefits of HIV Treatment for Dry-AMD Patients

In the November 21, 2014 issue of the journal Science, researchers from the University of Kentucky Medical Center published data implicating a newly recognized part of innate immunity—the inflammasome—and its possible role in retinal pigment epithelium (RPE) and macular degeneration. Investigators are hopeful that Nucleoside reverse transcriptase inhibitors (NRTIs) will be easily and widely adopted effective therapeutics for dry AMD. Most NRTIs are off-patent and inexpensive, and the safety profiles of later-generation NRTIs are well documented through decades of clinical experience in hundreds of thousands (or millions) of patients. This should facilitate a relatively rapid effort to translate these compounds for human use.

Researching Topical Squalamine Lactate for Wet AMD

Winter 2014

Squalamine lactate was originally identified as a broad-spectrum antimicrobial agent active against gram-positive and -negative bacteria, fungi, and protozoa. It was later discovered that squalamine inhibits angiogenesis by binding calmodulin, which is required for downstream signaling of several angiogenic factors including VEGF, platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF).1

Squalamine was developed as an intravenous drug and has been shown to inhibit choroidal and solid-tumor neovascularization. High doses of intravenous squalamine, however, are associated

with hepatotoxicity, fatigue, nausea, anorexia, and neuromuscular symptoms.2 Given the concerns over systemic safety and the unique ability to treat choroidal neovascularization locally, researchers developed a topical ophthalmic formulation of squalamine lactate.

Ohr Pharmaceutical, Inc. (New York, NY) conducted a phase 2, double-masked, randomized proof-of-concept trial comparing topical squalamine lactate 0.2% BID with placebo in treatment-naïve eyes with wet AMD, known as the IMPACT study. Both classic and occult lesions were included with best-corrected visual acuity ranging from 20/40 to 20/320. The central retinal thickness was at least 300 microns. Diabetics were included in this trial.

‘Given the concerns over systemic safety and the unique ability to treat choroidal neovascularization locally, researchers developed a topical ophthalmic formulation of squalamine lactate.’

Interestingly, squalamine did not meet one of its primary objectives in this interim analysis: the topical formulation did not affect the number of ranibizumab injections given during this study. Groups received the same number of ranibizumab injections over 9 months (6.4 in the placebo group vs 6.2 in the squalamine group). However, the positive visual acuity results certainly warrant continuing with the trial.

‘Squalamine’s positive results for wet AMD demonstrate proof-of-concept, that a topical anti-angiogenic formulation achieves sufficient concentration and activity in the choroid to affect neovascularization.’

Squalamine’s positive results for wet AMD demonstrate proof of concept, that a topical anti-angiogenic formulation achieves sufficient concentration and activity in the choroid to affect neovascularization. Small studies also found encouraging preliminary results using squalamine for retinal vein occlusion-related macular edema, as well as for retinal neovascularization from proliferative diabetic retinopathy, further supporting squalamine’s efficacy as a topical formulation. Nonetheless, squalamine’s positive phase 2 interim results suggest that a topical eyedrop can be complementary to intravitreal ranibizumab and result in better visual acuity. That alone is a big step forward for our patients.

Premier Global Trends in Retina Survey Explores Medical Retina Treatment Choices

Winter 2014

The ASRS International Affairs and PAT Survey Committees thank the members of 25 retina societies from around the world who participated in the first Global Trends in Retina Survey—the widest-reaching retina survey ever conducted.

Part 2: Medical Retina Highlights

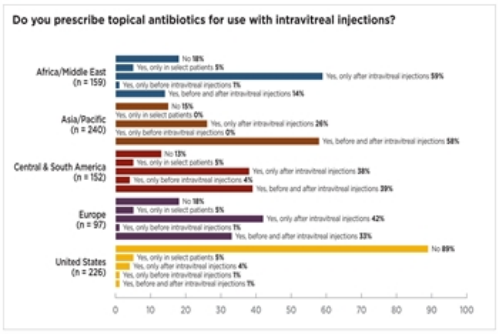
The fall Retina Times (available at www.asrs.org/retina-times) featured part 1 of the medical retina results. Here, we present part 2 of the highlights of responses to the survey's medical questions and compare them with US ASRS members' responses to the same questions.

To view the complete Global Trends in Retina Survey results online, visit http://www.asrs.org/international/global-trends-in-retina.

Responses below are grouped into 5 regions for ease of analysis. We also thank our thought leaders for participating in the following roundtable discussion of the survey results.

Do you prescribe topical antibiotics for use with intravitreal injections?

Anat Loewenstein—Africa/Middle East: There is a relatively high use of post-injection antibiotics in Africa and the Middle East compared with other regions. The reason may be that some of our patients go back to remote areas and may not have easy access to follow-up and treatment if needed. In most places, antibiotic use would also be easily reimbursed, so it can cause bias in favor of such presecription, even though all the evidence-based data point against it.



Enlarge

Alay Banker—Asia/Pacific: Due to the demographic differences in the Asia/Pacific patient population, there is a trend toward using topical antibiotics before as well as after injections. This is more so in most Asian countries where there is a large rural population; it is always thought to be prudent to give antibiotics to prevent infections.

André Gomes—Central and South America: In Brazil, intravitreal injections were approved under a code that allows you to bill a procedure done in the operating room. That was first thought to be for safety reasons, even though there are no specific guidelines from the Brazilian Retina and Vitreous Society to avoid an in-office injection.

The common use of antibiotic drops before or after intravitreal injections might be due to a combination of safety concerns and legal implications in case of endophthalmitis. Papers discussing its use are not very consistent and there is always the thought of "Why not?" That might help explain why topical antibiotics are so frequently advised in all of Central and South America.

José Garcia-Arumi—Europe: The use of antibiotics is very common in Europe, with 42% of respondents using them only after intravitreal injection, and 33% before and after—a total of 75% of respondents who treat with antibiotics, in contrast to 89% of respondents in the United States who do not.

Antibiotics are used mainly for legal issues; there is no scientific evidence that they decrease the risk of endophthalmitis. The use of gloves, sterile draping, a surgical mask, and antiseptics on conjunctiva and periocular skin are the most important measures for avoiding intraocular infection. Europe's results are more in the line with the other regions outside the United States.

Thomas Stone—United States: The United States seems to be the outlier in this question, and it's a trend that has grown over the past few years. A lot of the information from this has come from the DRCR.net studies, which have shown there may be a higher incidence of infection in those who take antibiotics than in those who don't.

What is your first-line therapy for a new phakic diabetic patient with VA=20/50 (reduced vision) and DME?

Anat Loewenstein—Africa/Middle East: Similar to many other countries, in Africa and the Middle East we start with bevacizumab. We may have more use of ranibizumab than other countries, probably because its use was approved earlier than in America, for example. In a phakic patient, most people would use an anti-VEGF as first-line therapy. Some of the payers do not pay for ranizibumab at all for this indication, so only bevacizumab is possible.

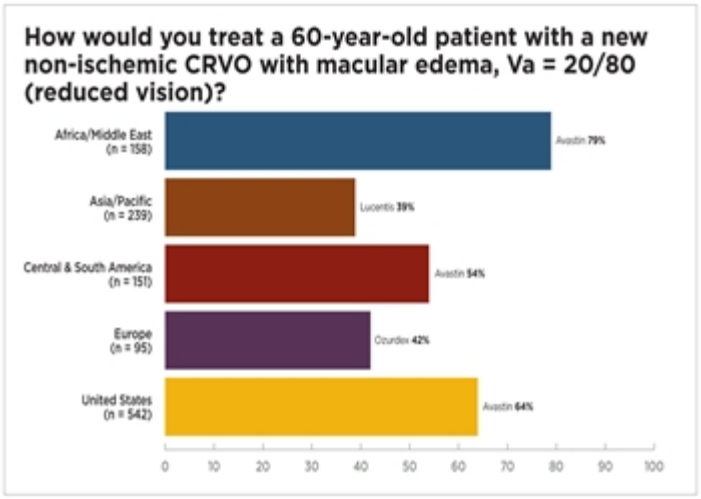
Alay Banker—Asia/Pacific: Just as in AMD, Lucentis (ranibizumab, Genentech, Inc, South San Francisco, CA) is used more than Avastin (bevacizumab, Genentech, Inc.) in the Asia/Pacific region to treat DME, and for the same reasons. However, the use of focal laser is still quite prevalent as it probably decreases the need for frequent injections.

The use of anti-VEGF injections will likely increase due to mounting evidence that injections may provide some visual benefit over laser, and that in the second and third year, patients might need fewer injections.

André Gomes—Central and South America: Retina specialists are still quite reluctant to abandon focal laser. One should state that the design of recent protocols that emphasized the better results of anti-VEGF over laser and or combination did not go deep enough to allow that. In my opinion, the cost and social burden of injections and the fact that you could minimize that by adding focal laser still haunts the minds of physicians across the world.

In Central and South America, combination anti-VEGF and laser might be one of the preferred options, but monotherapy with anti-VEGF drugs is being popularized. Also, we can better control the diabetes clinically and decrease the number of injections.

The choice of one drug vs the other depends on the public health care system of each country, and obviously the cost. The government does not automatically cover anti-VEGF treatment for DME in Brazil. Reimbursement by other health care providers is still a struggle we hope to overcome soon.



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José Garcia-Arumi—Europe: In Europe, Lucentis is still the most frequent pharmacological treatment, being the first-line therapy choice of 51% of respondents in the management of DME. Europe is the only geographical region in which Lucentis is preferred by more than half of the respondents. I think the reasons are the same as for AMD treatment.

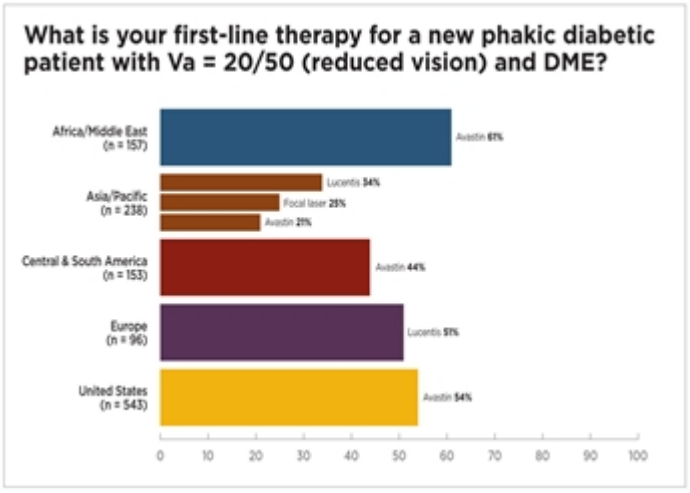
Focal laser is still a common treatment, but has decreased in importance in the last few years. Eylea is employed in only 1% of patients, probably because it has been approved for this indication very recently, and Avastin is employed in only 13% of patients. Intravitreal steroids are used in non-responder cases, which account for 10% to 15% of anti-VEGF therapy.

Thomas Stone—United States: The use of focal laser is steadily dropping as we become more comfortable with the results of anti-VEGF therapy. There's now a lot of evidence that the use of injections may provide some visual benefit over laser, and Avastin has been available longer than any other drug for this treatment. It will be interesting to see if the primary agent changes as more drugs have recently become available.

How would you treat a 60-year-old patient with a new non-ischemic CRVO with macular edema, VA = 20/80 (reduced vision)?

Anat Loewenstein—Africa/Middle East: In a patient with CRVO with edema and reduced vision, either an anti-VEGF or Ozurdex (dexamethasone intravitreal implant, Allergan, Inc, Irvine, CA) would be warranted. In some countries in Africa and the Middle East, you would need to start with 3 injections of bevacizumab and switch to either ranibizumab or Ozurdex as second line. Some of the payers allow also aflibercept as second line.

Alay Banker—Asia/Pacific: Similar to treating AMD, most physicians in the Asia/Pacific region prefer anti-VEGF injections. Also, because Ozurdex is not yet freely available in the majority of the countries, its use is still in the minority.



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André Gomes—Central and South America: Lucentis, Eylea, and Ozurdex (dexamethasone intravitreal implant, Allergan, Inc, Irvine, CA) are currently approved for venous occlusion in Brazil. Avastin and triamcinolone are off label. In this scenario, an anti-VEGF drug would be the natural choice. Ozurdex is quite new in our market and there is the issue involving cataract formation in phakic patients.

Reimbursement by the care providers is also a problem

, as we still do not have a specific code to bill them for treating venous occlusion. Again, Eylea is still new on board and its use should become more frequent over time.

José Garcia-Arumi—Europe: Ozurdex is the most common treatment in our region, preferred by 42% of European respondents; this is the opposite of the other regions, which employ anti-VEGF therapy. This delivery system of dexamethasone is employed between 1% and 5% in the other regions.

The reason Ozurdex is more frequently used in Europe is probably the longer duration of the effect in macular edema, the inflammatory component of the vein occlusion, and the sample of the ophthalmologists who answered the question. I think that anti-VEGF is employed more in acute cases, and Ozurdex is used in the follow-up to decrease the number of visits.

Thomas Stone—United States: These numbers for CRVO treatment mirror some of the drug-use frequency for wet macular degeneration. Avastin works well for CRVO. Because Avastin is fairly readily available, I believe there’s a comfort in using it for other diseases; its availability predated the use of the other agents, and it has become the most common treatment.

Point: There Is Evidence for Genetic Testing for AMD and the Use of the AREDS Supplements

About the usage of genetic testing before AREDS supplementation there are two idea. First, analysis, based on almost 40% of the patients who provided the basis of the AREDS recommendations, revealed dramatic differences in response to the AREDS formulation based on easily measured genetic risk. Investigators found these differences too large to ignore and chose to follow published treatment guidelines. At a minimum, doctors should consider withholding supplements containing high-dose zinc from patients in genotype group 2 (2 CFHand 0 ARMS2 risk alleles) until further studies are done. But other investigators do notrecommend genetic testing for AMD prior to administering AREDS supplements, but they endorse genetic testing for research purposes. They do not recommend therapy consisting of zinc alone or antioxidant alone, as the combination was better than either alone in all their AREDS analyses. They continue to recommend the combination of antioxidants and zinc (AREDS supplements) as the treatment of choice for persons with intermediate AMD (bilateral large drusen) or unilateral late AMD.

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