Hot Topics in Retina

- The paradigm shift in the diagnosis and management of diabetes
- Better Treatments for Wet AMD
- The search for a treatment for dry AMD — Are we getting closer?
- The emergence of OCT/OCTA imaging in retinal disease
- Targeted therapy for hereditary retinal disease

The Optometrist’s Role in Diagnosing and Managing Patients with Diabetes

- Optometrists play a critical role as a part of the healthcare team managing patients with diabetes
- It is paramount to recognize the presence of diabetic retinopathy
- Recognizing when it’s more than moderate nonproliferative diabetic retinopathy
- Accurate DR staging is critical for timely referral and treatment
  - Clinical exam vs. wide-field imaging

### ETDRS vs. International Classification of DR

<table>
<thead>
<tr>
<th>Diabetic Retinopathy</th>
<th>ETDRS</th>
<th>International Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild NPDR</td>
<td>At least one Ma</td>
<td>Less than Moderate</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>Higher standard than Ma or soft exudates, if IRMA</td>
<td>More than just Ma, but less than Severe</td>
</tr>
</tbody>
</table>
| Severe NPDR          | One of the following:  
  - Ma present in at least 2 quadrants  
  - IRMA present in at least 2 quadrants  
  - Standard photo 2A is at least 2 quadrants | One of the following:  
  - Ma present in all 4 quadrants  
  - IRMA present in at least 2 quadrants  
  - Prominent IRMA in at least 1 quadrant |
| PDR/High Risk PDR    | Severe NPDR and one of the following:  
  - Neovascularization  
  - Vitreous/preretinal hemorrhage | PDR/High Risk PDR |

#### 4-2-1 Rule

- 20 Hemorrhages & Ma in each 4 quadrants
- Significant venous beading in 2 quadrants
- Prominent IRMA in 1 quadrant

---

Mark Dunbar: Disclosure

- Optometry Consultant/Advisory Board for:  
  - Allergan  
  - Carl Zeiss Meditec  
  - Regeneron  
  - Genentech

Mark Dunbar does not own stock in any of the above companies
### Risk for Progression to PDR

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild NPDR</td>
<td>5%</td>
<td>13%</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>12%</td>
<td>33%</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>52%</td>
<td>60-75%</td>
</tr>
<tr>
<td>Very Severe NPDR</td>
<td>72%</td>
<td>75%</td>
</tr>
</tbody>
</table>


### Vision Loss in Diabetic Retinopathy

DME can develop at any stage – most likely to present as DME progresses.

Therapeutics (e.g. Anti-VEGFs)

### Diabetic Retinopathy Severity Scale

**International Scale**

- Mild NPDR
- Moderate NPDR
- Severe NPDR
- PDR

- Risk of vision loss increases

### Diabetic Macular Edema (DME)

- Thickening of the retina
- Secondary to leaky microaneurysms
- 99% of visual loss in diabetes

[SD-OCT of a retina with DME](#)

[Color Fundus photo with DME](#)
How we diagnose diabetic macular edema is changing

ETDRS definition has been modified in the era of OCT and anti-VEGF therapy

Diabetic Macular Edema (DME)

- CSME
- Center involved vs. Not center involved

2017 DME Classification: Center Involved or Not?

- ETDRS definition of "clinically significant macular edema" modified in era of OCT
- Randomized clinical trials of anti-VEGF agents used presence of DME in OCT central subfield

The ABC's of DME

- DCRR.net
  - Protocol I
  - Protocol T
- RISE
- RIDE
- READ
- VISTA
- VIVID
- Bolt

Essentially establishing the effectiveness of all the anti-VEGF drugs for the treatment of DME

DME Pre Treatment

Anti-VEGF Treatment

DME Post Treatment
The Debate...

- Is it better to treat early – before they develop PDR?
  - Would earlier treatment result in better visual outcomes?
  - Would it result in less # of injections?
  - Does the cost/burden of treatment warrant early treatment?

PANORAMA

- Phase 3 double-masked, randomized Prospective Study
- Efficacy and safety of intravitreal aflibercept (IAI) in patients with moderately severe to severe NPDR
  - DRSS 47 & 53
- Primary Endpoint:
  - Week 24
  - Proportion of patients improving ≥2 steps on DRSS
    - IAI groups combined
- Follow up through week 100

Wykoff, CC. Key points from the Phase 3 PANORAMA Study. (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.
Patients achieving a > 2 step improvement in ETDRS-DRSS Score at 52 and 100 Week

<table>
<thead>
<tr>
<th>Week 24</th>
<th>Week 52</th>
<th>Week 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept 2 mg every 16 weeks</td>
<td>58%</td>
<td>65%</td>
</tr>
<tr>
<td>Aflibercept 2 mg every 8 weeks</td>
<td>6%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Prevent the Development of PDR, ASNV, or CI-DME

**Progression to PDR or ASNV or Development of CI-DME Through Week 52**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Progression to PDR or ASNV or Development of CI-DME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept 2 mg every 16 weeks</td>
<td>4.0%</td>
</tr>
<tr>
<td>Aflibercept 2 mg every 8 weeks</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

Prevent the Development of PDR, ASNV, or CI-DME

**Week 100**

- 77% Aflibercept
- 76% Aflibercept
- 79% Aflibercept

**Diabetic Retinopathy Severity Score (DRSS)**

Level* ETDRS DRSS Severity Description
1 10 and 12 DR absent
2 14, 15, 20 DR questionable, microaneurysms only
3 35 Mild NPDR
4 43 Moderate NPDR
5 47 Moderately severe NPDR
6 53 Severe NPDR
7 60, 61 Mild PDR
8 65 Moderate PDR
9 71 High-risk PDR
10 75 High-risk PDR

**The main objective of this exploratory post hoc analysis of the RIDE and RISE clinical trials was to examine DR outcomes in patients who were at highest risk for progressing to PDR (baseline DRSS levels 47/53).**
RISE AND RIDE POST HOC ANALYSIS
PATIENTS WHO HAD NPDR AND PDR WITH DME

Post hoc analysis:
• Included 746 patients (LUCENTIS 0.3 mg, n=245; LUCENTIS 0.5 mg, n=247; sham, n=254) who had DR with DME and were randomized for treatment in RISE & RIDE
• DR outcomes with LUCENTIS were evaluated in patients along the spectrum of the severity scale (baseline ETDRS levels 10 – 75)
• Patients with prior panretinal photocoagulation (PRP) were not included in this analysis


LIMITATIONS OF THIS ANALYSIS INCLUDE THAT IT IS POST HOC (IE, NOT PRESPECIFIED IN PROTOCOLS). THE STATISTICAL SIGNIFICANCE OF THESE RESULTS CANNOT BE DETERMINED, AND THE CLINICAL SIGNIFICANCE OF THESE RESULTS IS UNKNOWN. RESULTS BETWEEN GROUPS SHOULD NOT BE COMPARED.

31

Ranibizumab induces Regression of Diabetic Retinopathy
Wykoff et al, Ophthalmology Retina October 2018

• At month 24, DR levels 47/53 80% of eyes had a 2-step improvement in ranibizumab treated eyes vs 12% in the sham treated eyes
• The regression of DR was not seen in earlier in less severe DR or in more severe DR
• Study Conclusion: In patients with baseline DR levels 47/53, ranibizumab treatment reduced the probability of patients experiencing a new proliferative event at month 36 by 3 times vs. sham treatment

Jama Ophthalmology, March 30, 2021

32

Protocol W: 2 Year Conclusions
Jama Ophthalmology, March 30, 2021

• The 2-year data did not confer visual acuity benefit compared to sham group
  Note: sham group received aflibercept once they developed DME or PDR
Is there a benefit from early Tx of Severe NPDR?

• So, what is the benefit of early treatment if it doesn’t result in any visual acuity improvement?

• Does it matter that there is a regression in DR if when all and said and done the patient ends up with the same visual outcome?

In-person expert examinations are impractical and unsustainable given the pandemic size of the diabetic population. As such, AI may offer a solution to this conundrum. DL, and specifically, deep convolutional neural networks (DCNNs), can be used for an end-to-end assessment of raw medical images to produce a target outcome prediction, the authors wrote.

August 6, 2020 FDA Clears EyeArt: AI System for Diabetic Retinopathy Detection

EyeArt is the first FDA cleared AI technology for autonomous detection of both more than mild and vision-threatening diabetic retinopathy. It is the most extensively validated autonomous AI technology tested in the real-world on more than half million patients and nearly two million retinal images globally.

In August 2020, EyeArt was FDA cleared as an AI system for diabetic retinopathy detection. The technology is designed to assist eye doctors in identifying diabetic retinopathy, a leading cause of blindness. The EyeArt system uses a deep learning algorithm to analyze retinal images and identify areas of diabetic retinopathy.

The technology was 87% sensitive and 90% specific for detecting more than mild diabetic retinopathy. The algorithm correctly identified 100% of patients with ETDRS level 43 or higher (moderate NPDR). The FDA clearance of EyeArt represents a significant advancement in the field of ophthalmology, as it provides an additional tool for doctors to help identify and manage diabetic retinopathy.
Age-related Macular Degeneration (AMD)

- Degenerative disorder that affects the macula
- Leading cause of legal blindness in people > 65 yo
- 90% of vision loss is 2 to CNV

ARMD

- Patients Affected
  - 90% dry or nonexudative
  - 10% wet or exudative
  - VA < 20/200
    - 80-90% exudative
    - 10-20% dry

AMD “Factoids”

- 1 in 3 people older than 75 will be affected by AMD
  - The number of people > 75 is steadily increasing
  - 10,000 people turn 65 in the US every day
- By 2025, there will be 44% more people in the US in this “high-risk” age group than there are today
Neovascular AMD: Risk Factors

- Emerging risk factors
  - Age
  - Race
  - Smoking
  - Family history
  - Variation in the complement factor H gene and other genes


What We Now Know

- Genetic background
- Environmental/lifestyle risk factors
- The interaction between these variables, predispose to AMD
- Treatments for wet AMD target VEGF – Hugely successful
- The future of AMD will target dry AMD

Current Hypothesis for AMD Pathophysiology

- Oxidative stress
- Genetic predisposition
- Environment

Complement deposition between retinal pigment epithelium (RPE) and Bruch’s membrane
- Loss of complement regulation
- Blood-retina barrier breakdown

Dry AMD → Geographic atrophy
Wet AMD

AMD Is the Leading Cause of Blindness for Caucasians in the US

- 53.9%
- 47.6%

AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; GA, geographic atrophy; nvAMD, neovascular AMD.


Anti-VEGF Standard of Care for Wet AMD

- Require frequent injections
- 1/3 of eyes develop atrophy
- Significant vision loss after 5–7 years of therapy
New Treatment for Wet AMD

• Beovu (Brolucizumab - Novartis)
  – Small size of the molecule allows higher dosing per volume results in a longer-lasting effect
• Abicipar (Allergan)
• Port Delivery System (Genentech)
  – Surgically implanted, refillable reservoir
  – Median time to first refill was 18 months
  • But large range: 7-8 months - 2 years

(Brolucizumab)

HAWK and HARRIER:
• 2 year randomized, double-masked, multicenter studies comparing the efficacy and safety of brolucizumab versus aflibercept in nAMD

Beovu (Brolucizumab)

HAWK and HARRIER:
• Dosing Schedule

Majority of Patients who Completed Week 48 on a q 12 Interval Remained on a q 12 Week Interval Until week 96 Completed
HAWK and HARRIER: Fewer patients on brolucizumab had IRF and/or SRF fluid at Weeks 16, 48, and 96.

Beovu (Brolucizumab)
- Received FDA approval October 7, 2019 for treatment of neovascular AMD
- Shortly after approval, the American Society of Retina Specialists (ASRS) began receiving reports of inflammation following intravitreal brolucizumab administration for NVAMD
- Several reported cases included retinal vasculitis that frequently resulted in vascular occlusion and significant vision loss

Abicipar (Allergan)
- Abicipar pegol is a DARPin directed to bind all VEGF-A isoforms, similar to ranibizumab
- It has a higher affinity and a longer half-life than ranibizumab (>13 days vs. 7.2 days) with longer duration and need for less frequent injections
- CEDAR and SEQUOIA
  - 90% had stability of vision
  - 6-8 injections vs. 13 ranibizumab injections at 52 week

Port Delivery System (Genentech)
- Surgically implanted, refillable reservoir
- Median time to first refill was 18 months
- But large range: 7-8 months - 2 years

Tx with Brolucizumab
- 50% of patients were maintained on q12 week dosing without requiring rescue treatments.
  - Eyes that could not be maintained on a regimen of q12 weeks tended to show a need for early re-treatment
- ~ 1/3 fewer patients (vs Lucentis) had fluid (IRF and/or SRF)
- At week 48, 31% fewer patients had IRF and/or SRF in HAWK, and 41% fewer in HARRIER (P < .0001 for both).
- Patients receiving brolucizumab 6 mg demonstrated superior reductions in central subfield thickness.
Port Delivery System (PDS)

- A permanent refillable eye implant that continuously delivers ranibizumab over a period of months
- Refilled every six months, PDS demonstrated non-inferior and equivalent efficacy compared to the standard of care—monthly ranibizumab eye injections
- Archway Study: Phase 3 results presented July 2020
  - Port delivery equivalent to monthly Ranibizumab injections
  - 248 pts PDS vs. 167 monthly injections
  - 98% did not need supplement injection

Wet AMD Patients Prefer PDS Implant Over Injections

Patients underwent only 2 procedures in 42 weeks.

- Patients with wet AMD who participated in Genentech’s phase 3 ARCHWAY trial strongly preferred the PDS sustained-release implant over regular injections of ranibizumab. More than 93% of the 228 patients who received the implant cited such reasons as fewer injections, reduced discomfort, and less nervousness and apprehension. All of the patients in the trial had been previously treated with anti-VEGF injections.
- Patients in the trial who did not receive the PDS had an average of 10 injections over 40 weeks, while those with the implant had only the initial implantation in the operating room and a mandated in-office refill at 24 weeks. Only 4 of 228 patients required a PDS refill prior to 24 weeks.
- At AAO Virtual 2020, Nancy Holekamp, MD, reported that the PDS with a custom formulation of ranibizumab provided essentially the same efficacy as monthly injections of regular ranibizumab. Vision and retinal thickness were both maintained with the PDS at basically the same level as with regular ranibizumab, although there was a wider variety of mild adverse events associated with the surgical procedure. The PDS is also currently in the phase 3 PAVILION trial for diabetic retinopathy and the phase 3 PAGODA trial for diabetic macular edema.

Holy Grail

- Treating Dry AMD and GA
  - Preventing it from progressing to Wet AMD

Key Genes Involved in the Development of AMD

- Accounts for 40-60% of AMD heritability

Potential Treatments for Geographic Atrophy

- APL-2: C3 inhibitor by Apellis
- Blocks all the pathways of complement activation

Filly 2 Trial

- Phase 2 FILLY trial: showed a 29% reduction in the growth of geographic atrophy lesions after 12 months in the monthly treatment group, and a 20% reduction in the every-other-month treatment group

Filly Key Takeaways

- APL-2 reduced the progression of GA in the largest Phase 2 GA trial (n=246)
- Results correlated treatment frequency with increasing effect size over time
- Upon discontinuation of APL-2 treatment effect declines

Filly Time Line and Endpoints

Lesion growth by 6 month periods (square root) – 18 months

APL-2 Shows GA growth at 12 months (square root)
18 Month Data

February 2018

• “The 18-month results of the FILLY trial support the positive effect seen at 12 months. In the FILLY trial, APL-2 significantly reduced the growth of GA, and may for the first time offer these patients hope of preserving their vision. We eagerly anticipate the start of the Phase 3 trials.”

Phase 3 Study: DERBY/OAKS

Dec 2018

• Company voluntarily implemented a temporary pause in dosing in the DERBY and OAKS Phase 3 trials due to observed cases of non-infectious inflammation in patients treated from a single manufacturing lot of APL-2 intravitreal drug product.

July 2020

News Release

April’s Complete Enrollment in Two Phase 3 Studies of the Targeted C3 Therapy, Regnecytis, in Patients with Geographic Atrophy (GA)

- April 2021
  - Preliminary phase 2A/D results available in Q1 2021
  - Top-line results expected in Q3 2021
  - Regnecytis targets C3 to control the uncontrollable growth in GA, a leading cause of blindness.

Risuteganib for Dry AMD

- Risuteganib is a small synthetic peptide that regulates integrin function
- Downregulates oxidative stress response and restores retinal homeostasis

Luminate (Risuteganib) Phase 2 Study

- 40 patients with intermediate dry AMD randomized to receive either intravitreal 1.0mg risuteganib or sham injection
- 48% of patients in Tx group vs. 7% in sham group had a > 8 letter improvement from baseline at 28 weeks
- The clinical trial met its primary endpoint
I was told there was nothing to do about my floaters?

“I am a 45 yo Male and am very bothered by floaters in my vision. They are constantly in my vision and interfere with may daily activities. I was told there was nothing I can do?”

Options for Treatment of Floaters

• Yag vitreolysis
• Pars plana vitrectomy

Important Considerations in Patients with Floaters

Are they acute or chronic?
• Acute Floaters – often from PVD
  – Usually resolve
• Chronic floaters that impact daily activities

The Ideal Candidate for Treatment of Floaters

Symptomatic
• Pseudophakic
• PVD

The NOT Ideal Candidate for Treatment of Floaters

• Young
• Phakic
• Attached vitreous
• High myope
Laser Vitreolysis for Floaters

- Done with a Yag
- Highly variable results
- Complications:
  - Cataract (hitting the lens)
  - Posterior capsule tears
  - Retinal burns
  - Foveal burns
  - Choroidal rupture
  - Choroidal hemorrhages
  - Retinal tear

Is Vitrectomy a Better Option?

- Smaller-gauge instruments (25 or 27) compared with the 20-gauge needles used less than 15 years ago
- Smaller vitrectomy instruments allow for sutureless procedures
  - Smaller sclerotomy
  - Trocars allow for small, thin-wall cannula
- Less inflammation
- Fewer complications
- Much greater success rate

Risk Factors for Vitrectomy

- Cataract
- Retinal tear or detachment
- ERM/Macular pucker
- Macular edema
- Endophthalmitis

Long-Term Follow-Up of Efficacy and Safety of YAG Vitreolysis for Symptomatic Weiss Ring Floaters

- 35 of 52 patients randomized to Yag vitreolysis or Control followed for 2.3 yrs
- 50% felt their symptoms were significantly or completely better at 6 mo
  - ~60% overall improvement in symptoms
- 3 patients developed retinal tears after 6 mo (not symptomatic)

Vitrectomy 2021

- 66 eyes in 52 patients (age = 63 ± 12 years) were included
- 36/66 (54.5%) eyes were phakic
- Average duration of coping was 30 months
- Etiology of floaters was PVD in 44/66 (67%), myopia in 19/66 (28%), asteroid hyalosis in 8/66 (12%)
- Retinopexy for retinal breaks occurring at the time of PVD was performed in 16 eyes (36% of all eyes with PVD; 24% of all eyes), a minimum of 3 months prior to vitrectomy
- PVD NOT induced and vitreous remained intact peripherally
- Main outcome: incidence of ret tears/detachments and cataract requiring surgery
Long-term Safety of Vitrectomy for Patients with Floaters

- Floater symptoms resolved in 65 of 66 eyes (98.5%)
- No patients (0/66; 0%) developed retinal breaks, hemorrhage, infection, or glaucoma (3 mo – 3 yrs)
- No retinal breaks/ detachments in the 22 patients without PVD pre-operatively (0/22 vs 9/30)
- Only 7/36 (19%) phakic eyes developed cataracts requiring surgery, an average of 16.5 months post-vitrectomy (7/36 vs 18/36 (50%)

Table 3: Postoperative Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. (n = 105 Eyes)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular leakage</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Closed retinal breaks</td>
<td>3</td>
<td>3.0</td>
</tr>
<tr>
<td>WVO</td>
<td>3</td>
<td>3.0</td>
</tr>
<tr>
<td>MAC</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Cataract</td>
<td>7</td>
<td>7.3</td>
</tr>
<tr>
<td>Retinal re-detachment</td>
<td>12</td>
<td>12.0</td>
</tr>
<tr>
<td>Corneal staphylococci</td>
<td>3</td>
<td>3.0</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>3</td>
<td>3.0</td>
</tr>
<tr>
<td>Iris (35 patients; PVD failed surgery)</td>
<td>2/35</td>
<td>6.1</td>
</tr>
<tr>
<td>Retinal pocket</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Methods
Limited vitrectomy with 35 gauge instruments was performed with or without PVD excision preserving 3 to 4 mm of vitreous base. Follow-up averaged 32.6 ± 23.3 months (range, 3–115 months), with 2 years or more in 144 eyes, 3 years or more in 68 eyes, 4 years or more in 51 eyes, and 6 years or more in 29 eyes.

Conclusions
Limited vitrectomy for macular edema due to vitreous hemorrhage, improved visual acuity, improved retinal function, and normalized OCT. The long-term efficacy and safety profiles suggest this may be a safe and effective treatment for clinically significant vitreous floaters, warranting a prospective randomized trial.

Hot Topics in Retina: Summary

- Exciting time for innovative treatments for retinal disease
- Paradigm shift in the management of diabetic retinopathy
  - Earlier treatments
  - Earlier referrals
- New Treatments for Wet AMD that may reduce the burden to treatments for patients
  - Emerging treatments in the pipeline for dry AMD
- We are witnessing the dawn of a new age in using genetics to treat eye disease
- Imaging continues to get better and better and important part of clinical practice