JOHNS HOPKINS MEDICINE eLITERATURE REVIEW

eOphthalmology Review

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Macula Society 2017 Updates: Polypoidal Choroidal Vasculopathy and Proliferative Diabetic Retinopathy

After participating in this activity, the participant will demonstrate the ability to:

- Evaluate how recent clinical research into anti-VEGF agents informs treatment for proliferative diabetic retinopathy.
- Discuss innovations in retina imaging, such as OCT or fundus autofluorescence that can improve diagnosis and treatment of retinal disease.

Guest Faculty Disclosure

Dr. Susan Bressler has disclosed that she has served as a principal investigator for Boehringer Ingelheim Vetmedica GmbH, Notal Vision Inc., and DRCR.net, and has served as co-investigator for Bayer and Novartis AG.

Dr. Gemmy Cheung has disclosed that she has served as a principal investigator for Bayer Corporation, Novartis AG, and Topcon. She has also served as a speaker for Allergan.

Unlabeled/Unapproved Uses

Dr. Bressler and Dr. Cheung have indicated that there will be no references to the unlabeled or unapproved uses of drugs or products in their discussion.

MEET THE AUTHORS

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10 Highlights from the Macula Society Meeting – 2017

1. Limitations of OCT-Angiography in AMD with Vascularized PED.
Salomon Cohen, Sandrine Tabary, Sarah Mrejen-Uretsky

Session II Neovascular AMD I: Wednesday, June 7, 2017; 5:41 PM

***e*Ophthalmology Summary:** In an observational study, 25 consecutive patients (6 males, 19 females, age range from 63 to 93 years) with either treatment-naïve or anti-VEGF treated vascularized pigment epithelial detachment (PED) with heights ranging from 268 to 1188 µm, mean: 476 µm, were evaluated by two senior retina specialists using either automated segmentation or manual segmentation of optical coherence tomography angiography (OCTA) images. Cases were included if fluorescein angiography documented the presence of a vascularized PED, and if structural OCT showed both a PED with a height>250 µm as well as either intraretinal fluid, subretinal fluid, or both. The detection rate of choroidal neovascularization for the first reader using automated slabs obtained from OCTA was 11 (44%) of 25 eyes, vs 19 (72%) of 25 eyes by the second reader using manually performed segmentations to review OCTA images. These results seem to be in contrast with the literature of OCTA in neovascular AMD, in which all subtypes of choroidal neovascularization were identified with a detection rate ranging from 85% to 100% of cases. These findings suggest that OCTA is less efficient in vascularized PED

compared with other subtypes of choroidal neovascularization, for directly visualizing the abnormal vascular flow that corresponds to type 1 CNV. The results also suggest that automated slabs of OCTA images should be interpreted with caution for diagnosing vascularized PED and that manual segmentations may improve the rate of detection of abnormal blood flow of CNV.

2. Acute Pseudophakic Cystoid Macular Edema Imaged by Optical Coherence Tomography Angiography.
Alain Gaudric, Sophie Bonnin, Aude Couturier, Lise Dubois, Ramin Tadayoni

Session V Vein Occlusion/Uveitis: Thursday, June 8, 2017 11:31 AM

***e*Ophthalmology Summary:** To study macular capillary changes and vessel density in acute pseudophakic cystoid macular edema (CME), a retrospective case-control study evaluated 8 eyes (7 patients) with pseudophakic CME and age-matched control eyes using optical coherence tomography angiography (OCTA) (RTVue XR Avanti; Optovue, Fremont, CA, USA). Vessel density of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) were calculated using an updated version of AngioAnalytic software **including the Projection Artifact Removal function**. The mean time of pseudophakic CME diagnosis was 2.3 ± 0.9 months after surgery. At the first examination, the vessel pattern was normal in the SCP and attenuated in the DCP. Mean vessel density of the SCP was 47.8 ± 3.8% in the study eyes, vs 52.9 ± 4.0% in the control eyes (P=.01), the difference was greater in the DCP layer (44.1 ± 7.4% vs. 54.2 ± 3.2%, P=.007). After resolution of the edema, the vessel pattern in the DCP recovered to normal and the vessel density in both plexuses was no longer different from that of the control eyes. The complete resolution of abnormal vessel patterns and density in acute pseudophakic CME highlights its potentially different pathophysiology from eyes with chronic vaso-occlusive diseases such as diabetic retinopathy or retinal vein occlusion.
Accepted for publication in RETINA

3. Lesion Shape as a Risk Factor for Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration.
Frank Holz, Maximilian Pfau, Monika Fleckenstein, Moritz Lindner, Lukas Goerdt, Srinivas Sadda, Matthais Schmid, Christopher Brittain, Erin Henry, Daniela Ferrara, Steffen Schmitz-Valckenberg

Session III Dry AMD: Thursday, June 8, 2017 8:24 AM

***e*Ophthalmology Summary:** To compare the prognostic value of lesion shape features with growth of geographic atrophy (GA) in age-related macular degeneration (AMD), the authors performed a longitudinal natural history study in 296 eyes of 201 patients with AMD that had GA. Baseline variables, including lesion area, perimeter and the Feret diameters (defined as the distance between the two parallel planes restricting the object perpendicular to that direction) on fundus autofluorescence (FAF) images were graded and evaluated for prediction of the square root lesion growth rate. The two-year results indicated that a single individual factor (i.e., square-root circularity) could explain up to 21% of the variability in growth rates and previous progression rates can explain 18.5% of the variability in upcoming progression rates. In this scenario, the models with square-root circularity (R2=0.379), square-root perimeter (R2=0.344), FAF pattern (R2=0.325), and focality (R2=0.335) were even more accurate in predicting growth rates. The findings herein confirm the potential importance of lesion shape as a prognostic variable for GA growth rates in addition to baseline lesion size, lesion location, multifocality, and fellow eye status.

4. Deep learning in the management of age-related macular degeneration.
Ursula Schmidt-Erfurth, Sebastian Waldstein, Hrvoje Bogunovic , Ferdinand Schlanitz, Georg Langs

Session IV Imaging: Thursday, June 8, 2017 9:33 AM

***e*Ophthalmology Summary:** Introducing deep learning, the authors reported the validation of automated computer algorithms for detection and quantification of potential morphologic biomarkers from a cross-sectional analysis of eyes with AMD, based on phenotyped data sets from 317 eyes with the intermediate stage of AMD, 317 with choroidal neovascularization (CNV), and 80 eyes with geographic atrophy (GA). Their results indicated that focal regression of drusen was associated with conversion to advanced AMD with 0.70/0.73 specificity/sensitivity. Disseminated hyperreflective foci in the outer retinal layer were indicative for progression to GA with 80% accuracy, while retinal layer alteration and focal hyperreflective foci over drusen were predictive of CNV development with 66% accuracy. In cases of advanced neovascular AMD, only intraretinal fluid had a moderate impact on functional outcomes and a 70% specificity and sensitivity could be achieved in predicting the retreatment need over 24 months. This study shows that comprehensive analysis of imaging biomarkers using deep learning methods may allow one to reliably estimate disease worsening and treatment response.

5. Efficacy and safety of ranibizumab versus verteporfin photodynamic therapy in Asian patients with myopic choroidal neovascularization: 12-month results from BRILLIANCE.
Timothy Lai, Youxin Chen, Arthur Foo, Renxin Lin, Anna Egger

Session VI Other Macular Diseases: Friday, June 9, 2017 8:41 AM

***e*Ophthalmology Summary:** The 12-month outcomes of the BRILLANCE study, which compared the efficacy and safety of ranibizumab 0.5mg versus verteporfin photodynamic therapy in Asian patients with myopic choroidal neovascularization, was reported. 457 patients were randomized 2:2:1 into Group (G) 1 (ranibizumab on day 1, Month 1 and thereafter as needed); G2 (ranibizumab on day 1 and thereafter as needed); or G3 (vPDT on day 1 and treated with ranibizumab or vPDT or both as needed from Month 3). Ranibizumab treatment in G1 (+9.5 letters) and G2 (+9.8 letters) was superior to vPDT +4.5 letters) with differences of G1-G3 = 5 letters (P<.001) and G2-G3 = 5.3 letters (P<.001) based on the mean average BCVA change from baseline to Month 1 through Month 3. The mean BCVA letter change from baseline at Month 12 was 12.0 (G1), 13.1 (G2) and 10.3 (G3). Up to Month 11, patients received a mean of 4.6 (G1), 3.9 (G2) and 2.6 (G3) ranibizumab injections. The results support the use of ranibizumab treatment, with re-treatment guided by visual stabilization or disease activity, over vPDT in Asian patients with myopic CNV at least up to Month 3.

6. Trends and Factors Associated with Diabetic Retinopathy Self-Awareness and Timeliness of Diabetic Eye Care over 6 Years.
Lloyd Aiello, Paolo Antonio Silva, Jerry Cavallerano, Jennifer Sun

Session VII Diabetic Retinopathy I: Friday, June 9, 2017 9:43 AM

***e*Ophthalmology Summary:** This study evaluated the extent of, and factors associated with, diabetic retinopathy (DR) self-awareness and timeliness of eye care follow-up over a 6-year period among 12,058 subjects with varying levels of ophthalmic provider specialization. Overall, DR awareness was associated with longer diabetes duration, vision-threatening DR, eye examination within 1 year, prior dilation, scheduled follow-up appointment and greater provider specialization. There was improved DR awareness and timeliness of follow-up during the 6-year period. However, a large proportion of unawareness and timeliness still existed when vision-threatening DR was present in this population, with 52% unaware that they had any DR and 88% not planning timely follow-up eye care relatively to having vision-threatening DR. Although rates appeared to be related to provider specialization, the discrepancy existed across all provider types (44%-87% unaware, 69%-93% not timely), suggesting that methods to enhance transfer and retention of eye care knowledge to diabetic patients are urgently needed.

7. Predictability of IOP Response in Patients Receiving Prior Steroid and Subsequent Administration of the 0.2 ug/day Fluocinolone Acetonide Intravitreal Implant.
Seenu Hariprasad, Clare Bailey

Session VIII Diabetic Retinopathy II: 10:34 AM Friday, June 9, 2017

***e*Ophthalmology Summary:** To assess the intraocular pressure (IOP) outcomes following fluocinolone implant (Iluvien®) therapy in eyes previously treated with an intravitreal corticosteroid, 345 eyes (from 305 patients) with DME having a mean follow-up of 428 days were identified by searching electronic medical records across 14 UK sites using the MedisoftTM audit tool of the U.K. EMR systems. After treatment with a fluocinolone implant, for those patients with no history of an IOP-related event after receiving corticosteroid, there were no cases of IOP>30 mmHg nor initiation of IOP-lowering medications. For those patients where an IOP elevation was observed following prior receipt of intravitreal corticosteroids, there was a greater incidence of IOP elevation or use of IOP-lowering medications. This predictability may provide an important clinical tool to mitigate the most common side effect associated with the use of the Fluocinolone Implant in the treatment of pseudophakic eyes with DME.

8. Preliminary Intravitreal Gene Therapy Safety Results for X-Linked Retinoschisis.
Mark Pennesi, Maria Parker, Paul Yang, David Birch, Jason Comander, Anthony Moore, Rabia Ozden

Session XI Tumors/Inherited Retinal Disorders: Saturday, June 10, 2017 8:17 AM

***e*Ophthalmology Summary:** In a safety report of intravitreal delivery of rAAV2tYF-CB-hRS1 for gene therapy in x-linked retinoschisis (XLRS), eleven patients, aged from 19 to 80 years old, with XLRS were enrolled in a Phase I/II dose escalation study. Group 1a and 1b subjects who received a dosage of 1 x 1011 vg/eye by intravitreal injection have completed at least 12 months of follow-up. Follow-up in Groups 2 (3 x 1011 vg/eye) and Groups 3 (6 x 1011 vg/eye) patients ranged from 1-11 months. There was no evidence of toxicity based on visual acuity measurements, perimetry, or ERG's, suggesting that intravitreal treatment with rAAV2tF-CB-hRS1 is well tolerated. Systemic laboratory studies did not identify any clinically meaningful abnormalities. The most common adverse ocular event was intraocular inflammation (anterior and posterior), which ranged from mild to moderate, and was controlled or resolved with or without the use of topical and/or oral corticosteroid treatment.

9. HDL-Cholesterol as Causal Risk Factor for Age-Related Macular Degeneration.
Tien Wong, Qiao Fan, Joseph C. Maranville, Caroline Chee, Runz Heiko, Ching-Yu Cheng

Session XIII Neovascular AMD II: 10:58 AM Saturday, June 10, 2017

***e*Ophthalmology Summary:** To investigate the potential role of plasma lipid levels in late AMD across multiethnic populations, the team selected 185 single nucleotide polymorphisms (SNPs) as instrumental variables associated with plasma lipids to evaluate 16,144 late AMD cases and 17,832 controls of European descent, together with 2,219 cases and 5,275 controls of Asian descent using a two-sample Mendelian randomization approach. They found that higher plasma HDL cholesterol was associated with an increased risk of late AMD in both Europeans and Asians, after accounting for pleiotropic effects with LDL cholesterol and triglycerides. Conversely, neither LDL cholesterol, nor triglyceride levels were associated with AMD. The study implicates HDL as a key factor in development of late AMD.

10. Augmented Reality Video Microscope (ARVM) for Retina Surgery as a Replacement of Operational Microscopes.
Anat Loewenstein, Amir Manor, Adiel Barak

Session XIV Vitreoretinal Surgery: Saturday, June 10, 2017 11:36 AM

***e*Ophthalmology Summary:** To test the augmented reality video microscope (ARVM) imaging quality and its impact on surgery visualization and to test intra-operative surgical assisting applications for improved surgery decision making, 5 patients for extraction of silicone oil from the vitreous cavity were studied in the primary part of the examination and during the surgery. The system's key parameters were refined to enhance performance related to surgery visualization, ergonomic and setup time. Related patient OCT data was displayed to the surgeon in real time in correspondence to the retina visualization produced from the ARVM. Results suggested good visualization of the posterior chamber was achieved using the ARVM. Digital image manipulation allowed control of image rotation, light parameters, digital zooming and image enhancement for optimal visualization of both the retina and vitreous cavity. The set-up time at the beginning of surgery was short and the adjustment of the head wearable display (HWD) was seemed relatively easy. The surgeon reported that the HWD did not impose any fatigue or stress on the head, and was judged to be comfortable by all participants. The use of

this HWD, the ultra-resolution stereoscopic cameras and computerized processing has the potential of improving the surgeon's images, enables supporting information to be visualized during surgery, and may enhance surgical performance.

OTHER RESOURCES

Download the podcast transcript

NEWSLETTER ARCHIVE SHARE WITH A COLLEAGUE

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Podcast Transcript

Welcome to this *e*Ophthalmology Review podcast. I'm Bob Busker, managing editor of the program. Today's discussion comes from the recently concluded 40th Annual Macula Society Meeting in Singapore, where findings about treating Proliferative Retinopathy, and imaging biomarkers for Polypoidal Choroidal Vasculopathy, were presented.

***e*Ophthalmology Review is presented by the Johns Hopkins University School of Medicine and is supported by educational grants from Genentech Inc, Regeneron Pharmaceuticals Inc, and Carl Zeiss Meditec. This activity has been developed for ophthalmologists and retina specialists. There are no fees or prerequisites to participate.**

Learning objectives for this activity include:

- **Evaluate how recent clinical research into anti-VEGF agents informs treatment for proliferative diabetic retinopathy; and**
- **Discuss innovations in retina imaging, such as OCT or fundus autofluorescence that can improve diagnosis and treatment of retinal disease.**

Our host is eOphthalmology Review course director, Dr. Neil Bressler. Dr. Bressler is the James P. Gills Professor of Ophthalmology and Chief of the Retina Division at the Wilmer Eye Institute at Johns Hopkins in Baltimore. Dr. Bressler has disclosed that he has served as a principal investigator for grants to Johns Hopkins University School of Medicine from Bayer Corporation, Novartis AG, Regeneron, Roche, and Samsung.

Dr. Bressler's first guest today is Dr. Susan Bressler, Professor of Ophthalmology at the Johns Hopkins University School of Medicine, to discuss her presentation: "Factors Associated with Worsening Proliferative Diabetic Retinopathy in Eyes Treated with Panretinal Photocoagulation or Ranibizumab."

Dr. Susan Bressler has disclosed that she has served as a principal investigator for Boehringer Ingelheim Vetmedica GmbH, Notal Vision Inc., and DRCR.net, and has served as co-investigator for Bayer and Novartis AG.

Dr. Susan Bressler and Dr. Neil Bressler have indicated that there will be no references to the unlabeled or unapproved uses of drugs or products in their discussion.

And now, from 40th Annual Macula Society Meeting in Singapore, Dr. Neil Bressler, with Dr. Susan Bressler.

NEIL BRESSLER: Thank you, Bob, and thank you Dr. Susan Bressler for taking the time to be with us today. Dr. Susan Bressler was presenting some important information at the 40th Macula Society Meeting being held this year in Singapore. She was discussing with us factors that are associated with worsening of proliferative diabetic retinopathy in eyes that were treated either with PRP, panretinal photocoagulation, or ranibizumab. Dr. Bressler, thank you for being with us today.

SUSAN BRESSLER: You're welcome. Thank you for having me.

NEIL BRESSLER: So tell me, why were you interested in pursuing this question in the first place? This is, as I understand,

part of DRCR Network Protocol S, maybe you can tell me what that protocol is all about first.

SUSAN BRESSLER: Sure. So Protocol S was really the first randomized prospective clinical trial that directly pitted our gold standard, panretinal photocoagulation, PRP, against an anti-VEGF approach to manage eyes that have proliferative diabetic retinopathy. And I think the results of Protocol S were very fascinating and helpful when we reported this in November 2015 in *JAMA*.

Essentially, Protocol S met all of its targets. First and foremost, it did demonstrate that using repeat intravitreal ranibizumab injections, eyes with proliferative retinopathy could avoid severe vision loss, and do so at about the same frequency with which we can accomplish that important goal with PRP. So by considering a new intervention, we are not sacrificing those critical vision outcomes where we are really stopping patients with proliferative disease from going on to blindness.

Second, we even identified that patients who were treated with ranibizumab had superior vision outcomes relative to PRP when we did a specific type of analysis called area under the curve, where we actually take into account the entirety of the 24 month course of an individual.

NEIL BRESSLER: So what were the differences in vision did you see?

SUSAN BRESSLER: Well, if you looked solely at the 24 month visit as though a patient walked in in January of 2014 and you fast forwarded to January of 2016, there was about a two letter difference between change from baseline in the eyes that were randomly assigned to ranibizumab, as compared to the eyes that were randomly assigned to PRP. And that difference, that average difference, met our noninferiority outcomes which was a margin of 5 letters.

NEIL BRESSLER: Assuming that the vision was no worse when you used ranibizumab compared with PRP laser for proliferative diabetic retinopathy, were there any advantages to giving the ranibizumab in this trial?

SUSAN BRESSLER: There were definite advantages. I mean we've known for 40 years that PRP has some inherent risks. Number one, it is a destructive treatment and we're sacrificing aspects of vision function. Notably, we're compromising visual field which was born out in Protocol S, and we are potentially exacerbating preexisting diabetic macular edema or inviting incident macular edema to develop.

So we had some secondary objectives to see whether or not ranibizumab would offer other advantages over PRP, assuming the visual outcomes were comparable, and we identified several. First, patients who were treated with ranibizumab were far less likely to go onto vitrectomy to manage their PDR. So one would avoid the morbidity and the costs associated with surgical intervention for PDR if one adopted an anti-VEGF approach at baseline.

NEIL BRESSLER: Were there others besides avoiding vitrectomy?

SUSAN BRESSLER: There were. Visual field, as we would have expected, was different between the two treatment arms. The PRP group lost a considerable amount of visual field when using a central and a peripheral automated visual field program, whereas, surprisingly, the eyes treated with ranibizumab had almost no change, whatsoever, in visual field. And then there was one other very important difference between the groups, which was development of center involved diabetic macular edema associated with vision impairment. Individuals who started without any macular edema, were three times more likely to develop visually impairing center involved DME if they were treated with PRP as compared rather than ranibizumab.

NEIL BRESSLER: Okay, I think I understand the background. So you had this trial of patients with proliferative retinopathy, they either got PRP laser or anti-VEGF with ranibizumab. The visions were not substantially different, there certainly was no harm to the vision, maybe a little better vision with ranibizumab, and then you preserved the visual field, you had less edema maybe that was forming, and it was just less likely to have to go on to vitrectomy.

So let's get to what the new data were that you were presenting, and that was looking at factors that were associated with worsening of the proliferative retinopathy while you were treating them with either PRP or ranibizumab. What do we mean by worsening proliferative diabetic retinopathy, what's worsening?

SUSAN BRESSLER: Well certainly worsening can be a visual deficit, but we've already addressed that by looking at the primary endpoint of the study and seeing that vision on average was preserved with either modality. But for worsening of PDR, we're basically evaluating anatomic targets. Does the eye go onto vitreous hemorrhage? Did the eye go onto retinal detachment, either tractional or rhegmatogenous? Was there a need for vitrectomy? Did the eye development anterior segment neovascularization or neovascular glaucoma? So we developed a composite outcome which was made up of those anatomic events signifying progression of the disease.

NEIL BRESSLER: Okay, for this composite outcome of complications or worsening of proliferative retinopathy, was there a difference in how often they occurred, with PRP vs ranibizumab?

SUSAN BRESSLER: There was. We looked at the cumulative probability of having this composite outcome in each of our treatment arms, PRP vs ranibizumab, and the cumulative probability of having PDR worsening was 34%

through two years in the eyes assigned to ranibizumab, and 42% in the eyes assigned to PRP. That equates to about a 30% greater increase in the hazard that an individual treated with PRP will have one of these untoward events, as compared to had they been treated with ranibizumab.

But even more importantly, when we looked at risk factors that were associated with worsening, we were able to identify that the most important risk factor was the severity of the proliferative retinopathy. And that's true whether they're treated with PRP or ranibizumab. The more severe the PDR to begin with, the more likely there will be progression of the PDR over time.

So when we compare the two treatment arms, PRP to ranibizumab, we adjust for the severity of proliferative disease at entry. And when we do that, the difference between the two treatments becomes even wider and statistically significant.

NEIL BRESSLER: So let's say that you're trying to avoid these worsening outcomes such as having a vitrectomy, or having a hemorrhage, or even neovascular glaucoma like you said, if you are trying to avoid them with the anti-VEGF treatment, does it make sense that you would see a difference? Because didn't some of the PRP eyes actually get anti-VEGF, as well, to treat concomitant DME that they may have had?

SUSAN BRESSLER: Yes, I mean that's a good point, that Protocol S is not as pure an experiment as one would love to do. And that reason is we permitted in protocol S individuals who simultaneously had both PDR and macular edema, creating a vision impairment. And at the time we started Protocol S, we felt it was the standard of care to address the maculopathy with anti-VEGF. So we certainly didn't want to withhold that therapy for the macular status among individuals who might be assigned randomly to the PRP arm to manage their proliferative disease.

So anyone who entered the trial, and it was about 1 out of four of our study eyes that entered the trial, with

macular edema and a vision impairment, had to receive, starting at time zero, ranibizumab to manage the macular edema, even if they were assigned to the PRP group.

So what we also did in this analysis is we looked at the large subgroup, 80% of all the study participants, who did not present with macular edema, so they were not required to receive ranibizumab in the PRP group, and looked at that treatment group comparison of PRP vs ranibizumab among these individuals who essentially are just walking in with PDR, and the differences in rates of PDR worsening were even greater in that subgroup favoring the ranibizumab approach.

NEIL BRESSLER: So let's recap. You had this trial looking at two different approaches to proliferative retinopathy, PRP, which has been used for over four decades, and this anti-VEGF with ranibizumab. And it appears that there are advantages, if you have access to it, to use the anti-VEGF. Now you're doing an additional analysis looking at factors that might be associated with this composite outcome of worsening of the proliferative retinopathy. What were the factors you found that were associated with worsening?

SUSAN BRESSLER: So the strongest factor was the severity of the proliferative disease when you initiate either one of these therapies. And I think that that's really important because, as we've shared the results of Protocol S with the worldwide ophthalmologic community, there's been some hesitancy to consider this management alternative, particularly in eyes that have greater levels of proliferative disease.

We hear people ask all the time, aren't you fearful that eyes with high risk PDR or even greater levels of PDR, will have a crunch in response to anti-VEGF administration and go on to vitreous hemorrhage, go onto retinal detachment.

That was one of the reasons we wanted to do this analysis, to be able to respond to that viewpoint. And what we demonstrated is you should be fearful because the greater the level of proliferative disease, the greater the probability that an eye will progress, but that is true, no matter what you do to that individual, PRP or anti-VEGF, and, in fact, if you do anti-VEGF,

they'll be less likely to have those untoward outcomes as compared to PRP.
NEIL BRESSLER: All right, so it may be that it's even a stronger argument, the worse the retinopathy, to consider this anti-VEGF therapy. I've heard some people say maybe the PRP laser that was given wasn't strong enough. Were there limitations to this study, was the PRP laser adequate?

SUSAN BRESSLER: Well I think that it was adequate and that it was a fair comparison of PRP as compared to anti-VEGF. We used the same protocol of PRP administration that was used in the Early Treatment Diabetic Retinopathy Study (ETDRS). So it's the same protocol that I believe most of us have been using in clinical practice for the last 30 years. Eighty percent of the patients assigned to PRP received conventional single spot laser to perform the PRP, and the protocol guidelines of the administration were 1,200 to 1,600 applications with a 500 micron spot size produced on the retina at a 0.1 second duration to have a light to medium whitish burn.

And I think that most people would accept that that's a standard PRP. And 98% of the patients assigned to PRP received laser to within the guidelines that we followed. Now one could say just because an investigator recorded administering 2,200 applications being administered, does that translate 1:1 to 2,200 500 micron spot sizes on the retina, and I would be at a loss to say I know with certainty that that's true. But we would have had the same uncertainty in the ETDRS and yet that is the protocol that's been proved effective and in use all these years.

NEIL BRESSLER: Well I think we've really gotten additional evidence to support the consideration of ranibizumab as an anti-VEGF treatment to be an alternative therapy for treating proliferative diabetic retinopathy. The factors that you showed us that are associated with the retinopathy worsening, appear to be the level or severity of the proliferative retinopathy and whether that gives you a worse outcome because you got anti-VEGF or because you had PRP. It sounds like it's less likely to run into those complications if you got anti-VEGF therapy, is that fair?

SUSAN BRESSLER: I think that's fair and I think that it just reminds us that no matter which modality you use, these patients need to be carefully monitored. Just because you've done either ranibizumab or PRP, does not mean that trouble isn't brewing ahead. Even in the ranibizumab group, rates of worsening were 30 to 34%. So patients need to remain under care so that if there is still activity of the proliferative disease, one can supplement the treatment with whichever intervention you have decided to commit that patient to. And, of course, even consider crossing over from one modality to another. At the end of the day, we're looking for an anatomic endpoint to foster regression of the proliferative disease to decrease the likelihood of vitreous hemorrhage, of traction detachment, of vision loss.

NEIL BRESSLER: Well thank you, Dr. Susan Bressler, for being with us today, sharing your Macular Society presentation on factors associated with worsening of proliferative diabetic retinopathy when people get anti-VEGF or PRP laser to treat that, and we're just very thankful that you could continue to give us more information on that today.

SUSAN BRESSLER: It's a pleasure and I hope we'll have more to share in the future.

NEIL BRESSLER: We want to tell you about a new feature of our eOphthalmology Review Podcasts, and then I'll be back.

BOB:
Hello, I'm Bob Busker, managing editor of eOphthalmology Review. I'd like to take a moment to tell you about a new feature we've added to this program.

The amount of important new information about advances in retinal care that's presented at every major ophthalmology meeting is more than we're able to discuss through these podcasts.

So to help keep you more fully informed, we now offer "eOphthalmology Review Conference Highlights" — a quick overview of 10 other important developments in retinal science featured at each of our attended conferences.

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Once again, to access our website, please go to www.eophthalmologyreview.org. Thank you.

BOB:
Welcome back to this *e*Ophthalmology Review podcast, reporting from the 2017 Macula Society Meeting in Singapore. Dr. Neil Bressler's next guest is Dr. Gemmy Cheung — Associate Professor at the Singapore National Eye Center — to discuss her presentation on "Multimodal Imaging Biomarkers In Polypoidal Choroidal Vasculopathy".

Dr. Cheung has disclosed that she has served as a principal investigator for Bayer Corporation, Novartis AG, and Topcon. She has also served as a speaker for Allergan.

Dr. Cheung and Dr. Bressler have indicated that there will be no references to the unlabeled or unapproved uses of

drugs or products in their discussion.

Dr. Bressler?

NEIL BRESSLER: Thank you, Bob, and thank you, Dr. Gemmy Cheung for joining me today.
GEMMI CHEUNG: Hi, Neil, thank you very much, and welcome to Singapore.

NEIL BRESSLER: It's a pleasure being here and we're going to discuss with Dr. Cheung a presentation that she made at the 40th anniversary annual meeting of the Macula Society. And this was on multimodal imaging biomarkers in polypoidal choroidal vasculopathy. Gemmy, maybe I can turn to you first and ask why were you pursuing this in the first place? Why try to identify biomarkers in PCV?

GEMMY CHEUNG: Thank you. We've heard a lot of clinical evidence and also from our daily clinical practice we've witnessed that anti-VEGF is working very well in many of our patients. However, a couple of years ago with an increasing analysis, a lot from the CAT study, of imaging biomarkers that are additionally helpful for us to predict which patients may respond better to other patients. However, this is particularly in patients with typical CNV.

Now coming back to our Asian population, there are some notable differences between our population and those, for example, seen in CAT. For example, we have a big proportion of patients with the PCV subtype and we know that the clinical features include a lot of massive hemorrhage. So that could be one factor how it may change the visual outcome and also in terms of the incidence of other structural factors such as fibrosis and macular atrophy development, as well.

The other important feature is, obviously, we see less of the typical drusen, particularly pseudo drusen, another risk factor for atrophy and perhaps important in predicting visual outcome. So we were particularly interested to look at the imaging biomarker features in our population using multimodal imaging.

NEIL BRESSLER: Okay, I think I understand. So we had a lot of studies that came out of North America or Europe that looked at treatment of choroidal neovascularization and macular degeneration using anti-VEGF, and then trying to look at whether there are predictors of responses that you might see in clinical trials that

evaluated this. But this may not apply to predictors of response, perhaps in the Asian populations where more than they have this feature or type of choroidal neovascularization that's a polypoidal choroidal vasculopathy variant, is that right?

GEMMY CHEUNG: Correct.

NEIL BRESSLER: Okay. So when you first say multimodal imaging, what are you talking about, what are these multiple images that you obtain?
GEMMY CHEUNG: So if we look at what has been published, for example, geographic atrophy or macular atrophy, subretinal hyperreflective material, fibrosis, some of these have been described. But when we look at the methodology, it's quite interesting because some studies have used color fundus photograph or fluorescein angiography, whereas newer imaging has been generally using OCT. And a lot of the times each individual feature has been graded in isolation. So we would like to use a combined approach of the various imaging modalities, including color fundus photograph, autofluorescence, fluorescein angiography, in our

population, particularly indocyanine green angiography, and also SD OCT. And at the same time we developed a very extensive grading protocol to look at not just one or two features individually, but to look at multiple features altogether and look at the interactions on the final visual outcome.
NEIL BRESSLER: All right, it sounds like you used many ways of imaging the retina to see if any or all of them might have some prediction of the response to anti-VEGF to treat. So what did you find, did more than one of these modalities predict vision outcomes in patients?

GEMMY CHEUNG: Yes, indeed. First of all, before we come to the results, I think it's important to go through the methodology because one of the biggest outcomes that we got out of this exercise was developing and validating the imaging grading protocol which took a lot of effort, both from our side, the Singapore team who graded mainly the color fundus photograph, fluorescein and indocyanine green angiography, and autofluorescence, and we collaborated with the Duke Reading Center who has expertise in grading the CAT study, amongst many other trials. And they graded many of the SD OCT qualitative and quantitative factors.

So each team graded their modalities individually, first of all, and then we combined all the results together and we found that I think most of the grading results, for example, on our endpoints, which were atrophy, fibrosis, subretinal hyperreflective material, they are in agreement in the majority.

There are a few cases that were discrepant dependant on the modality. And in these cases we had an open arbitration within the team, and we could resolve most of these discrepancies. So now, I think this is a very valuable tool with

established working methodology and we can go ahead and grade many other eyes and many other features.

NEIL BRESSLER: So it sounds like these different modalities might have been graded independent of one another, someone might have looked at the spectral domain OCT but not necessarily know what the ICG was showing.
GEMMY CHEUNG: Exactly. And I think that masking is important because it makes sure that each individual grading is not affected by the other modality.

NEIL BRESSLER: So how many people did you look at in this, what was the number of cases that actually had these multiple images that were obtained at baseline and presumably helped predict the vision outcomes at follow-up?

GEMMY CHEUNG: For the current presentation it is a pilot study so we only presented the first 50 cases with baseline and year 1 outcomes. But in the whole project, we are in the process of grading another 300 cases, so we look forward to reporting the full outcome.

NEIL BRESSLER: And did all 50 of these cases have this pattern of polypoidal choroidal vasculopathy?

GEMMY CHEUNG: No, about 60% of them have PCV, and the majority of the rest had typical AMD. We also have less than 5% with type 3 neovascularization.

NEIL BRESSLER: Were you looking just at the natural history of these eyes, or these were all being treated with an anti-VEGF agent or even with something else like photodynamic therapy?

GEMMY CHEUNG: Yes, all the patients underwent anti-VEGF therapy, and in addition, a proportion of patients had combination therapy with photodynamic therapy.

NEIL BRESSLER: And let's talk about then what the outcomes were. I presume you were looking first at predictors of vision outcomes, is that correct?

GEMMY CHEUNG: Yes, PCV outcome is the primary endpoint we wanted to look at, and after performing multivariable, stepwise linear regression, we reported that five individual factors were significantly associated with worse visual outcome. And these five factors were: presence of macular atrophy involving the fovea at baseline, presence of outer retina hyperreflective foci at baseline, presence of pigment epithelial detachment or sub RPE fluid to represent the same thing, and the final factor is presence of type 3 neovascularization.

Interestingly, we also looked at other factors which were not associated with final visual outcome, including age, the addition of photodynamic therapy, and a number of PGF anti-VEGF injections.

NEIL BRESSLER: Now you mentioned having type 3 neovascularization might be a predictive factor. What modality was that identified on and what do you mean by type 3 neovascularization for our audience?

GEMMY CHEUNG: What I mean by type 3 neovascularization is in another terminology is retinal angiomatous proliferation, or RAP in short. So the mode we used to identify RAP included the combination of FA and ICGA and SD OCT.

NEIL BRESSLER: And for some of these other features like the pigment epithelial detachment or subretinal fluid, what modalities were those identified on? Was it just one modality or if more than one modality could identify this, how was that handled?

GEMMY CHEUNG: The key to our current project is we tried to identify each mode using multimodality and we looked for consensus between different modalities. So, for example, with pigment epithelia detachment, one could easily identify that on SD OCT, I think that would

be the simplest methodology. But when we compare with color fundus photograph and FA, often these will confirm the findings.

NEIL BRESSLER: And you also mentioned that macular atrophy in the center of the posterior pole is predictive of a worse outcome. I would think sometimes it's hard to look in an eye that has choroidal neovascularization and determine is there atrophy there. So was this identified on OCT where there was missing pigment epithelium, or was it identified as we typically think of identifying atrophy looking at a fundus photograph?

Gemmy CHEUNG: Again, we based this on multimodal imaging and indeed I agree with you that grading of macular atrophy is not the easiest and most straightforward task, and it is an evolving area, as well.
So for this we performed a literature search and looked at how more traditional papers graded atrophy based on color fundus photography, fluorescein angiography, which shows you window defects, and also fundus autofluorescence. In addition, recently the classification of macular atrophy group, the CAM group, also published a paper which they recommended multimodal imaging criteria which incorporated significant findings from SD OCT on which you tend to see hybrid transmission of the light signals through to the choroid and a loss or thinning of the outer retinal layer.

So when we combine all these modalities, we find that actually the SD OCT was the most sensitive single modality, but again, I emphasize that when we put together all the different modalities, we try to aim for consensus and we look for agreement between the different modes.

NEIL BRESSLER: When you're looking for a predictor of a bad response, as in this case, what's the magnitude of the prediction that you could do with the several features that you identified on multivariate regression analysis? Was it a big predictor? Was it a moderate predictor? Was it a little predictor? What were each of these in terms of the magnitude of predicting a bad response?

Gemmy CHEUNG: Yes. For the pilot study we analyzed the finally BCBA as a continuous variable and we found that for most of the factors that we identified as important influencing factors, the magnitude we're talking about was a beta coefficient of about -3 to -6. So I think that is quite significant.

NEIL BRESSLER: Well I think those are very important bits of information. You said that this was just based on 50 people so far. What are your plans going forward, are you going to look at 100, are you looking at multiple sites beyond your eye center, what's the next step?
Gemmy CHEUNG: Well the immediate next step we are already in the process of grading the second batch of eyes, and in total we aim to complete grading in 300 cases. For the first pilot study we have merely reported on mainly the qualitative factors, so for the next stage we will report on even more details, qualitative and quantitative factors. And in addition, not only can we look at the biomarkers for predicting visual outcomes, we would also be able to inform ourselves of other important features such as what is the incidence of macular atrophy in our population. Bear in mind that photodynamic therapy, for example, is still quite commonly used in this area of the world, so that remains our concern whether photodynamic therapy may or may not affect the incidence of geographic atrophy, for example. So there are many possibilities.

NEIL BRESSLER: As I understand it, these factors that you identify as predictive or perhaps a bad response, are to help guide the expectations of the patient. They don't necessarily tell us we should avoid treating somebody with anti-VEGF, do they?

Gemmy CHEUNG: No, of course not. I think actually overall, as we've seen in the majority of anti-VEGF treated series and clinical studies, the majority of patients actually do have some improvement in vision.

NEIL BRESSLER: Well I really want to thank you for sharing this information with us. I recognize that this was a preliminary look at these multimodal imaging factors that might be predictive of responses in polypoidal choroidal vasculopathy, treated with anti-VEGF, or adding photodynamic therapy in some of these cases. It truly does expand our understanding since previously our predictive factors were based on most cases not having a polypoidal choroidal vasculopathy variant, but as you said, at least in this part of the world, but also throughout Europe, North America, and the other continents we do see cases of polypoidal choroidal vasculopathy. So think this will be very helpful in guiding our patients regarding their expectations and in guiding the ophthalmologist as to what to expect moving forward.

So thank you very much for sharing your presentation at the Macula Society with us today.

Gemmy CHEUNG: Thank you very much, Neil, it is my pleasure.

NEIL BRESSLER: Now, let's quickly summarize our discussion today in light of our learning objectives. The first learning objective was to evaluate how recent clinical research into anti-VEGF agents informs or teaches us about treating proliferative diabetic retinopathy.

We learned from Dr. Susan Bressler about additional analyses that were done from Protocol S in the Diabetic Retinopathy Clinical Research Network. This protocol compared using either panretinal photocoagulation or anti-VEGF therapy with ranibizumab to treat proliferative diabetic retinopathy. Dr. Susan Bressler reviewed with us some of the outcomes that previously had been reported to suggest anti-VEGF may be a viable alternative therapy for proliferative retinopathy, including similar or maybe slightly better vision outcomes with anti-VEGF, less visual field loss, and less chance of going on to vitrectomy or developing macular edema that needs anti-VEGF therapy.

Dr. Bressler expanded on these findings by looking at what factors might be predictive or associated with worsening of proliferative diabetic retinopathy, and we learned that actually the worse the level or severity of the proliferative retinopathy, the greater the benefits might be with anti-VEGF therapy.

Our second learning objective was to discuss innovations in retina imaging such as spectral domain OCT, fundus autofluorescence, coupled with fundus photographs, fluorescein angiography, and indocyanine green angiography, among patients that have polypoidal choroidal vasculopathy in an Asian population.

Dr. Gemmy Cheung informed us that, in fact, there may be factors using multimodal imaging that can be predictive of the response that you'll see when you treat these eyes at least with anti-VEGF, sometimes with photodynamic therapy, as well. And by combining all of this imaging information, we may be able to guide our ophthalmologists, as well as our patients as

to what's a more likely scenario that could lead to a worse outcome or a less likely scenario for that part. This was a preliminary study that she shared with us and is planning to extend that more so in the future.

So I want to thank both of my guests, Dr. Susan Bressler from the Johns Hopkins University School of Medicine, and Dr. Gemmy Cheung from the Singapore National Eye Center, for sharing their insights with us today.
Neil BRESSLER: I'm Dr. Neil Bressler from the Johns Hopkins University School of Medicine, we're sharing this information with you from the 40th Anniversary Annual Meeting of the Macula Society, this year being held in Singapore, and we'll be returning soon with our next eOphthalmology podcast in August from the American Society of Retina Specialists Meeting to be held in Boston. Thank you very much.

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