JOHNS HOPKINS MEDICINE eLITERATURE REVIEW

eOphthalmology Review

Provided by the Johns Hopkins University School of Medicine

Vol 4: Supported by educational grants from Genentech, Regeneron Pharmaceuticals, and Carl Zeiss Meditec, Inc.

VOLUME 4 - ISSUE 3

LISTEN TO PODCAST | DOWNLOAD PODCAST | PHYSICIAN POST-TEST

Advances in Management of Choroidal Neovascularization

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

- S ummarize new developments in the identification and treatment of Myopic Choroidal Neovascularization.
- Describe how early diagnosis and treatment of AMD improves clinical outcomes.
- Identify patients for appropriate anti-VEGF treatments based on available therapies and the latest data.

Guest Faculty Disclosure

Dr. Colin Tan has disclosed that he has served as a conference speaker for Bayer and Novartis AG, and served on an advisory board for Novartis AG.

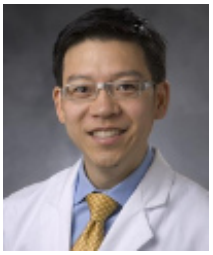
D r. Paul Hahn has disclosed that he has served as a consultant from Second Sight Medical Products, Inc., and served on an advisory board for Genentech, Inc.

Unlabeled/Unapproved Uses

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

MEET THE AUTHORS

Colin Tan, MBBS, MMed, FRCSEd
Associate Professor of Ophthalmology
National Healthcare Group Eye Institute
Tan Tock Seun Hospital
Singapore



Paul Hahn, MD, PhD
Associate, NJRetina
Paramus, New Jersey

Release Date:
October 12, 2017

Expiration Date:
October 11, 2019

LISTEN TO PODCAST NOW | DOWNLOAD PODCAST | SUBSCRIBE NOW | PHYSICIAN POST-TEST

10 Highlights from ASRS 2017

1. Optical Coherence Tomography Features Preceding the Onset of Advanced Age-Related Macular Degeneration
Johanna Seddon, MD, ScM

AMD 1 Symposium: Saturday, Aug 12, 2017; 8:30 AM

***e*Ophthalmology Summary:** To identify optical coherence tomography (OCT) biomarkers to predict progression of age-related macular degeneration (AMD), a prospective epidemiologic study followed up 40 eyes of "progressors" (transitioned from the early or intermediate stage to the advanced AMD, i.e., choroidal neovascularization [CNV] or geographic atrophy [GA] involving the center of the macula) and 40 eyes of non-progressors with a mean duration of 5.4 years. Neurosensory retinal thickness abnormalities (odds ratios [ORs]: 19.2 to 72.6; $P < .001$) and disruption of the ellipsoid zone (ORs: 17.9 and 30.6; $P < .001$) were found to be significantly associated with higher odds of progression to advanced AMD. Drusenoid detachment of the retinal pigment epithelium (RPE), RPE thickening, pigmentary hyperreflective material and choroidal abnormalities were associated with a 5 to 7 times increased risk of progression. Systematic assessment of OCT features of the early or intermediate stage of AMD showed that abnormalities at the level of photoreceptors, RPE and choroid are associated with progression to both GA and CNV. These findings provide insights into mechanisms of AMD progression, and suggest a potential similar disease mechanism for the 2 subtypes of advanced AMD.

2. RGX-314 Gene Therapy Subretinal Delivery for the Treatment of Neovascular Age-Related Macular Degeneration (nAMD)
Jeffrey Heier, MD

AMD 1 Symposium: Saturday, Aug 12, 2017; 8:50 AM

***e*Ophthalmology Summary:** The trial design, challenges and experience of the Phase 1 RGX-314 (an AAV8 vector delivering an anti-VEGF fab protein) trial, a surgical gene therapy to treat neovascular age-related macular degeneration (nAMD), were discussed at the ASRS 2017 Annual Meeting. The investigators developed an automated subretinal delivery process to deliver the gene therapy construct using an animal wet lab procedure. The Phase 1 study will evaluate 3 doses of RGX-314 in a dose escalation with 6 subjects per arm. Subjects who respond to anti-VEGF therapy will receive gene therapy and be followed for 24 months to evaluate safety and evidence of a biologic effect. The procedure includes standardized vitrectomy and an automated injection of 250 microlitres using a MedOne Microdose Injector syringe within the subretinal space outside of the temporal vascular arcades. RGX-314 gene therapy has potential to minimize the treatment burden of frequent intravitreous injections for nAMD.

3. Vision Preference Value Scale and Patient Preferences in Choosing Therapy for Symptomatic Vitreomacular Interface Abnormality
Adrienne Scott, MD B

Macular Pucker Symposium: Saturday, Aug 12, 2017; 11:30 AM

***e*Ophthalmology Summary:** To assess a vision preference value scale and patients' preferences in choosing therapy for symptomatic vitreomacular interface abnormality (VIA) among patients across 3 continents, a cross-sectional questionnaire study was performed among 213 patients (include 100 epiretinal membranes, 100 macular holes and 14 vitreomacular traction) from the U.S., United Kingdom, and Thailand with symptomatic VIA diagnosed within 1 year and visual acuity (VA) less than 20/20. The mean vision preference value (0-1: death to perfect health) was 0.759 (± SD 0.146) without differences identified among the 3 VIA types. Lower vision preference value was associated with lower VA in the better-seeing eye (r=0.11; 95% CI: 0.028, 0.199; $P = 0.01$), blurry vision (r=-0.07; 95% CI: -0.121, -0.025; $P = 0.003$), and at UK ($P = 0.012$) and Thailand ($P = 0.022$) sites. Patients with higher VA in the affected eye have lower enthusiasm for vitrectomy (OR=0.22; 95% CI: 0.09, 0.52; $P = 0.001$), versus people have blurry vision (OR=3.14; 95% CI: 1.37, 7.17; $P = 0.007$). More patients were enthusiastic about vitrectomy (71.1%) compared with intravitreous injection (56.9%) (95% CI: 5.16%, 23.3%; $P = 0.002$). The data suggest that patients have similar preference values among 3 types of symptomatic VIA, and have slightly more enthusiasm for vitrectomy.

4. Optical Coherence Tomography Angiography in Retinopathy of Prematurity
J. Campbell, MD, MPH

Pediatric Symposium: Saturday, Aug 12, 2017; 1:25 PM

***e*Ophthalmology Summary:** To evaluate the role of optical coherence tomography angiography (OCTA) in the clinical diagnosis of retinopathy of prematurity (ROP), Dr. Campbell's team designed a 100 kHz swept source OCTA system with a novel prototype handheld probe for use in the neonatal intensive care unit. Using this device, they are in the process of acquiring data in patients, focusing on determination of zone 1 disease, rapid structural OCT and OCTA of peripheral stage, and total retinal blood flow (TRBF) in all stages of disease and plus disease. The ultimate hope is that OCT/OCTA can provide objective diagnosis of zone, stage, and plus disease in ROP. So far, OCTA findings have suggested its ability to differentiate active vs regressed extra-retinal neovascularization, while wide-field OCT might provide structural information that is potentially useful in aiding ROP diagnoses.

5. Potential Safety Concerns of Bevacizumab for Retinopathy of Prematurity
Robert Avery, MD

Pediatric Symposium: Saturday, Aug 12, 2017; 2:01 PM

***e*Ophthalmology Summary:** To evaluate potential systemic effects of off-label bevacizumab for retinopathy of prematurity (ROP), studies were assessed looking for reports of systemic effects. Two studies of neurodevelopment in ROP babies raise concern that bevacizumab use could contribute to developmental impairment relative to laser use alone. There are reports of bevacizumab injection for ROP causing effects on fellow un-injected eyes, as well as reports of reduced cerebral blood flow after bevacizumab injection for ROP. Pharmacokinetic studies in ROP have shown a maximum serum concentration at 2 weeks almost 10-fold higher than reported in adults. Serum VEGF in babies with ROP is reduced for at least 8 weeks, and other cytokines, some which could affect lung development, are

affected as well. Ranibizumab has a much lower systemic exposure that bevacizumab, and may have a slightly shorter duration of effect in ROP than bevacizumab. These reports raised the concerns of potential harm of using bevacizumab in ROP treatment. Randomized clinical trials are indicated to evaluate laser, bevacizumab, and ranibizumab in the treatment of ROP.

6. Adalimumab in Noninfectious Uveitis of Idiopathic Etiology—Efficacy Across Different Anatomical Locations the VISUAL I and VISUAL II Trials
Pauline Merrill, MD

Inflammatory & Infectious Diseases Symposium: Sunday, Aug 13, 2017; 9:00 AM

***e*Ophthalmology Summary:** Efficacy of adalimumab, a TNF inhibitor, in patients diagnosed with idiopathic uveitis and stratified by anatomical location of uveitis at study entry in two global phase 3, double-masked trials, VISUAL I (active uveitis) and VISUAL II trials (inactive uveitis), was assessed. Patients received placebo or adalimumab subcutaneously (80 mg week 0, followed by 40 mg every other week from week 1 up to 80 weeks). The primary endpoint was time to treatment failure at or after week 6 for VISUAL I; and at or after week 2 for VISUAL II. The efficacy of adalimumab was significantly greater than placebo in idiopathic uveitis overall in both VISUAL I (81) and VISUAL II (69) trials. Point estimate results favored adalimumab in intermediate (HR 0.83; 0.31-2.18), posterior (HR 0.15; 0.02-1.27) and pan-uveitis (HR 0.50; 0.23-1.08) patients, but the hazard ratio crossed 1.00, precluding definitive confidence of a difference. No new safety concerns were raised, but the presenter noted that patients need to be tested for tuberculosis, be free of demyelinating disease, and be aware of an increased, although low, rate of malignancy associated with this treatment. The data show high efficacy of adalimumab in both active and inactive idiopathic uveitis patients despite the variance of anatomical location of the diseases.

7. The SAKURA Study: Corticosteroid Tapering Success With Every-Other-Month Intravitreal Sirolimus for Noninfectious Uveitis of the Posterior Segment
Alay Banker, MD

Inflammatory & Infectious Diseases Symposium: Sunday, Aug 13, 2017; 9:05 AM

***e*Ophthalmology Summary:** The Phase III multinational, randomized, double-masked SAKURA program, was comprised of two studies (one pivotal, included 347 subjects; one supportive, included 245 subjects) assessing the efficacy and safety of every-other-month intravitreal sirolimus (mTOR inhibitor, 440 µg vs 44 µg) injections in subjects with active non-infectious uveitis of the posterior segment. The proportion of subjects achieving systemic corticosteroid tapering success (overall prednisone-equivalent dose ≤5 mg/d at Month 5 without rescue therapy) in conjunction with improvements in vitreous haze was assessed at Month 5. 46 (22.1%) subjects from the 440 µg group and 32 (15.4%) subjects from the 44 µg group formed the Intent-to-Taper population. In the integrated Intent-to-Taper population, 21.2% vs 13.5% of subjects (440 vs 44 µg, respectively) achieved the primary endpoint of no vitreous haze (VH 0) at Month 5 ($P = .038$), 43.5% (20/46) vs 28.1% (9/32) of subjects (440 vs 44 µg, respectively) achieved vitreous haze reduction (VH 0/0.5+) ($P = .168$), and 69.6% (32/46) vs 68.8% (22/32) of subjects in the 440 µg vs 44 µg groups achieved tapering success at Month 5 ($P = .939$). The SAKURA Program show that intravitreal treatment with 440 µg sirolimus led to significant improvements in vitreous haze and more successful tapering of oral corticosteroids in patients with noninfectious uveitis of the posterior segment.

8. Silicone Oil Droplets Are More Common in Fluid From BD Insulin Syringes As Compared To Other Syringes
Geoffrey Emerson, MD, PhD
Presumed Silicone Oil Droplets in the Vitreous Cavity after Intravitreal Bevacizumab Injection With Insulin Syringes
Rahul Khurana, MD

AMD2 Symposium: Monday, Aug 14, 2017; 8:08, 8:13 AM

***e*Ophthalmology Summary:** During 2016, the ASRS received numerous reports of silicone oil droplets after intravitreous injection, primarily associated with insulin syringes with a fixed needle. To determine if silicone oil droplets are more common in Becton Dickenson (BD) Insulin Syringes as compared to other syringes, BD insulin syringes, BD tuberculin syringes, Henke Sass Wolf (HSW) insulin syringes, and HSW silicone free syringes (20 of each) were evaluated by loading with 0.06 mL of fluorescein ophthalmic solution (Bausch & Lomb) and incubated at 4 °C for 2-4 weeks. Syringe fluid was ejected onto slides, sampled at the beginning, middle, and end of injection from the syringe and examined microscopically for air and oil droplets. Silicone oil droplets were identified in 5 (25%) (all from the end of injection) of the BD insulin syringes; no oil droplets were found in BD tuberculin syringes, HSW insulin syringes, or HSW silicone-free syringes (ANOVA, $P < .05$). Air bubbles were visible in the majority of samples from all types of syringes without differences identified (ANOVA, $P = 0.2$ and 0.36 for BD and HSW, respectively). The results demonstrate that oil droplets are most commonly observed with BD insulin syringes, especially when the plunger is depressed maximally.

9. Ozurdex vs Ranibizumab vs Combination for Central Retinal Vein Occlusion (ORION)
Victor Gonzalez, MD

Retinal Vascular Symposium: Tuesday, Aug 15, 2017; 10:06 AM

***e*Ophthalmology Summary:** To compare the effect of dexamethasone intravitreal implant, ranibizumab, and the combination of the two in the treatment of macular edema secondary to central retinal vein occlusion (CRVO), a multicentered randomized masked clinical trial enrolled 34 subjects comparing dexamethasone implant alone (14 subjects) every 16 weeks, ranibizumab alone (11 subjects) every 4 weeks, and the combination of dexamethasone implant every 16 weeks and ranibizumab (9 subjects) according to reinjection parameters assessed monthly through week 20. There was no difference identified in the change in best corrected visual acuity (BCVA) (mean 16.8 vs 18.5 letters, $P = .67$) nor in the change in central retinal thickness (CRT) (mean -408 vs -486 µm, $P = .56$) between ranibizumab and combination, nor difference in BCVA (mean 13.2 vs 18.5 letters, $P = .36$) and in CRT (mean -376 vs -486 µm, $P = .50$) between dexamethasone implant and combination. The dexamethasone group received a mean injection of 2 vs 3.5 in the combination group and 6

in the ranibizumab group ($P < 0.01$). The results among a small number of study participants could not identify a difference in structural or functional outcomes between ranibizumab, dexamethasone implant, or the combination of both at 24 weeks in the treatment of macular edema secondary to CRVO while the combination group had fewer injections.

10. Topline Results From Prospective, Double-Masked Phase 2b Clinical Trial Evaluating ALG-1001 (Luminate®) Compared to Bevacizumab in Patients With DME
David Boyer, MD

Proliferative Diabetic Retinopathy: Tuesday, Aug 15, 2017; 3:55 PM

***e*Ophthalmology Summary:** The safety and efficacy of a Phase 2b, clinical trial using ALG-1001 (a synthetic RGD-class oligopeptide, integrin receptor inhibitor) to treat patients with centrally-involved diabetic macular edema (DME) was reported. 136 patients with DME involving the fovea, visual acuity of 20/40 to 20/320 (Snellen equivalent), and central 1-mm macular subfield thickness of ≥350 µm on spectral-domain optical coherence tomography (SD-OCT) from 32 U.S. sites were randomly assigned to four groups. Groups received 1.0, 2.0, or 3.0mg of ALG-1001 (3 monthly intravitreal injections at week 0, 4, and 8) or 1.25mg of bevacizumab (6 consecutive monthly injections). At Week 20, the mean (SD) change in BCVA were 5.2 (6.86), 2.7 (7.31), -1.5 (9.97) and 7.0 (8.21) letters gained in 1.0, 2.0 and 3.0mg ALG-1001 versus 1.25mg bevacizumab, respectively. The mean (SD) change in CMT were -77 (141), -16 (110), -1 (152) and -104 (107) µm, respectively. There were no drug related serious adverse events in the ALG-1001 groups. The results suggest that three doses of anti-integrin ALG-1001 monotherapy demonstrate non-inferiority to 6 doses of bevacizumab (≤ 3 letter difference in BCVA and ≤ 30µm difference in CMT) in patients with DME at week 20.

OTHER RESOURCES

Download the podcast transcript

NEWSLETTER ARCHIVE SHARE WITH A COLLEAGUE

PROGRAM DIRECTOR

Neil Bressler, MD
James P. Gills Professor of Ophthalmology Chief of the Retina Division
Wilmer Eye Institute at Johns Hopkins
Baltimore, Maryland

PROGRAM PLANNER

Jun Kong, MD, PhD
Post-Doctoral Clinical Research Fellow
Wilmer Eye Institute Johns Hopkins Hospital
Baltimore, Maryland

Podcast Transcript

BOB BUSKER:
Welcome to this *e*Ophthalmology Review podcast. I'm Bob Busker, managing editor of the program. Today's discussion comes from the recently concluded 35th Annual American Society of Retina Specialists Meeting in Boston, where results from the Phase III RADIANCE Trial, as well as the 12-Month Results of EVEREST II, 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 In.c, 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:

- **Summarize new developments in the identification and treatment of Myopic Choroidal Neovascularization.**
- **Describe how early diagnosis and treatment of AMD improves clinical outcomes.**
- **Identify patients appropriate for anti-VEGF treatments based on available therapies and the most current data.**

Our host is *e*Ophthalmology 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. Colin Tan, Associate Professor of Ophthalmology at the Duke National University of Singapore Medical School, to discuss his presentation of the 12-Month Results of EVEREST II.

Dr. Colin Tan has disclosed that he has served as a conference speaker for Bayer and Novartis AG, and served on an advisory board for Novartis AG.

Dr. Colin Tan 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 beyond the agents and procedures specifically described in the trial.

And now — from 35th Annual ASRS Meeting in Boston — Dr. Neil Bressler, with Dr. Colin Tan.

DR. BRESSLER: Thank you, Bob, and thank you, Colin, for joining me today at the 35th Annual American Society of Retina Specialists Meeting being held in Boston. I appreciate your sharing with us some of the important information from the EVEREST II trial. Please give me a little background on why this trial was even done in the first place. I know we were trying to treat patients who have perhaps a polypoidal choroidal vasculopathy pattern of macular degeneration, but what was the EVEREST II trial looking at in those patients?

DR. TAN: Thank you very much, Dr. Bressler, it's great to be here with everyone. The EVEREST II study was planned to evaluate both the visual acuity outcomes and the polypoidal rates among patients with polypoidal choroidal vasculopathy. We know from EVEREST 1 that patients who receive photodynamic therapy either with ranibizumab or alone had superior polypoidal rates compared to ranibizumab monotherapy. And from our experience, we feel that not only is the visual acuity important, but also the polypoidal rates, which is why the EVEREST II study was designed to evaluate both the visual acuity as well as the polyp closures.

DR. BRESSLER: That's interesting. I would have thought that if a patient has good visual acuity they might not care whether their polypoidal lesion was open or closed on ICG angiography. Aside from the visual acuity, what made you or the other investigators believe that also closing the polypoidal lesions might be of importance in managing these patients?

DR. TAN: There are two reasons why closure of the polyps would be important. First, the polyps are a source of leakage, and if we were able to close the polyps early with photodynamic therapy, potentially this could reduce the number of injections that the patients required.

We know in using anti-VEGF injections, one of the issues is the burden of injections where patients had to come back up to every month for injection, and we could reduce the injection, load for the patient, this potentially could be useful. In addition, the polyps, besides leaking, also are a source of hemorrhage in some cases. Not so common, they could have a very massive hemorrhage spontaneously. It's the concern for about hemorrhage, and we feel that it would be better if we had to close active polyps that we would close those.

DR. BRESSLER: I understand. So we have this perhaps variant of macular degeneration or choroidal neovascularization, this PCV or polypoidal choroidal vasculopathy. We know that we typically want to use anti-VEGF therapy for these, and you were investigating whether patients were randomly assigned to anti-VEGF therapy using ranibizumab alone, or whether there is added advantage to use ranibizumab along with photodynamic therapy that might be directed at the polypoidal lesion.

If that was the design, what did you find?

DR. TAN: The result at the 12 month primary endpoint was to examine both visual acuity and polyp closure. I'll talk first about visual acuity. The combination group of PCV and anti-VEGF gained about 8.3 letters. In contrast, the ranibizumab group gained 5.1 letters. That's about a three letter difference, and it was statistically significant.

Initially we looked at whether it was noninferior, and it was. Then the planned analysis went on to look at whether it was superior. We found that the gains were superior for the combination group.

DR. BRESSLER: So we are confident that the visual acuity was different or somewhat superior in the combination group.

DR. TAN: That's right.

DR. BRESSLER: All right, what else did you look at then?

DR. TAN: We also looked at the polyp closure rates, and from month 3 through month 12, the polyp closure rate for the combination group was about 70%. It was about 25% for month 3 for the ranibizumab monotherapy group, and it increased to about 35% at month 12, but it was still about half of that in the combination group.

DR. BRESSLER: So the polypoidal lesions, even with ranibizumab alone, may no longer be apparent by year, but twice as often if up to 70% of the time you no longer could see the polypoidal lesions the same way you did at baseline when you looked on ICG angiography at one year.

DR. TAN: Yes, that's correct.

DR. BRESSLER: And you think that may translate into fewer injections or less bleeding. How many injections did each group have?

DR. TAN: The median number of injections for the combination group was four compared to seven for the monotherapy group.

DR. BRESSLER: Three fewer injections. How many PDT sessions did they need? A patient might think, I need fewer injections but how many actual procedures do I get? How many injections on average do they get of PDT sessions?

DR. TAN: Well over 60% of them had only one PDT, which was the very first one at the start of treatment. If you count those with two PDT treatments, that was almost more than 90% of the entire cohort. Very few PDT sessions were required.

DR. BRESSLER: So the visual acuity difference was definitively superior in the combination group. Do we know if that has relevance to the patient — are substantially more people gaining a lot of vision? Or did substantially fewer patients lose a lot of vision? What did you find when you looked beyond the mean change at the percentage of the two groups who gained or lost a substantial amount?

DR. TAN: I don't have the numbers offhand.

DR. BRESSLER: That's fine. We often find that it's important to understand not only are the visions different, but how much are those differences clinically relevant? We'll look forward to hearing more information in the future.

Another thing we think about as we compare treatments, is whether they're equally safe. Obviously, the people who get fewer injections have a smaller chance of getting endophthalmitis. That's such a rare event now, I hope one in 5,000 in many places in the world, but were there other safety issues? Were there any differences in safety issues between the two groups?

DR. TAN: In the one year analysis we found no major safety signals. Both groups had very good outcomes. The endophthalmitis rate is very low, and the major finding was retinal hemorrhage or vitreous hemorrhage. There were possibly a few more cases in the monotherapy group than in the PDT group. This could just be the natural course of the disease and not necessarily related to the treatment.

DR. BRESSLER: So you found no increased harm or safety issues with the combination of ranibizumab and photodynamic therapy, is that correct?

DR. TAN: Yes, that's correct.

DR. BRESSLER: You mentioned several times that these results were seen in this randomized trial out to one year. Are the patients being followed for longer than that, or did they exit this trial after one year?

DR. TAN: The full duration of the study is 24 months, so the patients will be followed after month 12. We also have data on that, and we expect this data to be coming out within the next few months.

DR. BRESSLER: That's exciting, because we often learn whether differences were maintained through two years or whether there might be any other differences seen. What was the reason for following these people beyond one year, and does their treatment remain the same in that second year?

DR. TAN: The reason for following them beyond one year was precisely as you suggested: we need to look at the patients' clinical outcomes and visual outcomes beyond the short term. For example, EVEREST 1, which was the first randomized controlled trial on PCV, followed the patients only for six months, and that was one of the shortcomings of that study. EVEREST II wanted to address the short duration, and we found that a 24 month study was appropriate.

Because of the one year results, all patients at the end of the one year were switched to combination therapy. So because of different enrollment times, we have one group who had combination therapy all the way, one group who had ranibizumab and then was switched to combination therapy, and finally one group that was on ranibizumab monotherapy all the way because they had already completed the study by the time the first year results were available.

DR. BRESSLER: If a patient at 25% or 30% by one year in the ranibizumab monotherapy group no longer had any appearance of polypoidal lesions, can I assume they did not receive photodynamic therapy because there'd be no place to put it, or did you put it where you saw the polypoidal lesions from baseline?

DR. TAN: No, the repeat photodynamic therapy was only performed on patients who had polyps demonstrated by indocyanine green angiography. The protocol states that only if polyps were seen on the ICG angiogram do we consider photodynamic therapy. If there were no polyps and only the branching vascular network, then all patients received only ranibizumab monotherapy.

DR. BRESSLER: Let's close with thinking about this in the universe of studies that look at this.

So as I understand, another study uses a different anti-VEGF agent, aflibercept, in a study called PLANET. That also looked at the role of anti-VEGF, in this case in eyes that have polypoidal choroidal vasculopathy, but the anti-VEGF agent was aflibercept. Are there other differences, or how does that study fit side by side with EVEREST II?

DR. TAN: There haven't been any head to head studies on aflibercept vs ranibizumab, and that's one gap we hope can be addressed in the near future where we can have a head to head study between the two drugs. That would be very interesting.

But the PLANET study definitely has interesting results. Its design is very different from EVEREST 2, so we can't really compare them directly. PLANET was designed to treat all patients with aflibercept monotherapy for the first treatments and then assess whether any of them at three months required rescue PDT. They had some specific criteria to determine whether the patient would require rescue PDT, which is why at three months less than 10% of the patients required photodynamic therapy.

EVEREST II, in contrast, intended from the start to compare PDT and ranibizumab to ranibizumab monotherapy. There is still discussion and debate whether PDT is necessary, and if it is, should you consider this right from the start or treat later only if anti-VEGF doesn't work.

These studies give us different sides of the equation, and first we'll need to compare them head to head and also assess which treatment modality is the best.

DR. BRESSLER: So they're really complementary. They're asking different questions. EVEREST II compares photodynamic therapy combined with an anti-VEGF agent, in this case ranibizumab from the start, to ranibizumab alone. PLANET looks at a group of patients who all are assigned aflibercept for at least three months, and then there's a subsequent random assignment to let's say, rescue photodynamic therapy or not, or whether they were assigned to the group that could receive a rescue therapy.

Each study will guide us in managing polypoidal choroidal vasculopathy and not necessarily compare whether one anti-VEGF agent or the other is the one to use in polypoidal choroidal vasculopathy, is that correct?

DR. TAN: Yes, that's absolutely correct.

DR. BRESSLER: Thank you for taking time out of the busy schedule at the ASRS meeting here in Boston to share some of the new information that you presented our colleagues at the meeting on EVEREST II.

DR. TAN: Thank you, Dr. Bressler, for this opportunity, it's great to participate in this, and this is a great meeting.

MR. BUSKER:

Welcome back to this *e*Ophthalmology Review podcast, reporting from the 35th Annual ASRS Meeting in Boston. Dr. Neil Bressler's next guest is Dr. Paul Hahn, an associate with NJRetina, to discuss his presentation on Myopic Choroidal Neovascularization and the Results from the Phase III RADIANCE Trial.

Dr. Hahn has disclosed that he has served as a consultant for Second Sight Medical Products, Inc., and served on an advisory board for Genentech, Inc.

Dr. Hahn and Dr. Bressler have indicated that there will be no references to the unlabeled or unapproved uses of drugs or products in their discussion beyond the agents and procedures specifically described in the trial.

Dr. Bressler?

DR. BRESSLER: Thank you, Bob, and thank you, Paul, for joining me today here at the American Society of Retina Specialists' 35 Annual Meeting in Boston. We've asked you to discuss some of the exciting information you're presenting from the RADIANCE study. Let's start with your explanation of what the RADIANCE study is, what group of patients are we looking at with a retina problem.

DR. HAHN: Thanks, Neil, it's a pleasure to join you today. The RADIANCE trial was the phase 3 trial comparing ranibizumab to photodynamic therapy for treating patients with myopic choroidal neovascularization.

DR. BRESSLER: A decade ago we would treat all these patients with photodynamic therapy and wouldn't think of treating them with anti-VEGF therapy because we didn't have any evidence for that. Why then are we now comparing these two — did we know that one was better than the other before you did this study?

DR. HAHN: Photodynamic therapy in the US is currently the only FDA approved treatment option. As you alluded to in the past, that was really the only option that was really tried, but studies have shown that photodynamic therapy is not perhaps a great option for patients with myopic choroidal neovascularization.

At one year there is a signal of perhaps improved loss of vision, but at two years that didn't seem to pan out. Anecdotally over the next 10 years, as our experiences with anti-VEGF have developed, we all know that anti-VEGF appears to work for this condition, and RADIANCE was a phase 3 trial looking at ranibizumab to demonstrate this.

DR. BRESSLER: Now we really want to know when the patient walks in with pathologic myopia, has some vision loss and we decide from our imaging that loss of vision is from choroidal neovascularization. We want to learn whether we should be starting with photodynamic therapy or starting with anti-VEGF, or what. What did you find?

DR. HAHN: Those results are probably not surprising. Any retina specialist who practices currently is probably aware that anti-VEGF treatment should be better than photodynamic therapy, and I think most retina specialists would not use photodynamic therapy currently as first line treatment for myopic choroidal neovascularization.

The RADIANCE trial really supported those experiences. Ranibizumab was found superior to photodynamic therapy for visual acuity outcomes. At month 3, patients who received ranibizumab improved approximately 12 letters, whereas at month 3 patients who received photodynamic therapy at baseline improved about 1-1/2 letters, consistent with our anecdotal experiences.

DR. BRESSLER: So on average they didn't lose vision with photodynamic therapy; you just didn't see as substantial a gain, is that correct?

DR. HAHN: That's exactly right.

DR. BRESSLER: Typically in macular degeneration we think we need outcomes at least to a year, if not longer, though with pathologic myopia we tend to think a lot of the action occurs in the first few months. After three months did you compare how these two groups were doing?

DR. HAHN: Out to 12 months, the study identified that patients who received ranibizumab up front demonstrated sustained improvement. Those 12 letters improved to about 14 letters out to month 12.

In patients who received photodynamic therapy at baseline, at month 3 they were allowed to receive rescue therapy with ranibizumab at the investigator's discretion. And those patients improved from approximately 1.5 letters with photodynamic therapy alone, and over the next nine months out to month 12 they gained approximately nine letters improvement. That demonstrates that ranibizumab treatment, even with initial photodynamic therapy, can provide improvements, but as we see with other trials of anti-VEGF agents, those data also suggest that early treatment is of value.

DR. BRESSLER: That would suggest not necessarily starting that person on photodynamic therapy and if they don't do well give them anti-VEGF, or maybe start with anti-VEGF from the get-go, is that correct?

DR. HAHN: That would certainly be my recommendation.

DR. BRESSLER: It's often hard to determine if we still need to treat someone with choroidal neovascularization from pathologic myopia. It's hard to visualize these vessels, it's hard to tell if they're still leaking. What was used in the trial to decide if somebody should be retreated after three months with the anti-VEGF therapy?

DR. HAHN: The RADIANCE trial was very interesting in that in contrast to many other phase 3 trials, it did not look at monthly dosing with ranibizumab. I think this highlights our understanding that pathologic myopia and myopic choroidal neovascularization is different than macular degeneration, for example, which as we understand it does require chronic therapy.

This trial had two ranibizumab arms, both of which were retreated based on as-needed criteria. In the first arm, patients were retreated based on stability of visual acuity, which for technical reasons was determined over two preceding visits. At baseline patients were given a dose of ranibizumab and at month 1 received a dose of ranibizumab. All patients received two monthly doses of ranibizumab and subsequently monthly, but were retreated as needed based on changes in visual acuity.

In the second arm, patients were given ranibizumab at baseline and then followed monthly with retreatment based on disease activity, which was defined as fluid on OCT or leakage on angiography.

With these two retreatment groups, patients were compared to see which group fared better. It was actually a noninferiority test at month 6, and both groups were found to be equivalent in visual acuity outcomes. Interestingly, the number of injections was slightly different between the two. The median number of injections with the visual acuity retreatment arm was four, and the median number of injections in the disease activity arm was two. This is perhaps partly due to the

difference in loading doses that were required; the group with the higher median number of injections at four required two loading doses up front, and the other group with a median injection of two required only a single loading dose up front.

DR. BRESSLER: I like this a lot because when using visual acuity as a measure of should I retreat, you looked at the last two visits, because the visions might fluctuate. They're hard to measure in anyone, but certainly difficult in someone who has pathologic myopia. So by using two, you wanted to be confident whether you really should consider retreating.

Then you also looked at the possibility of imaging to see if that guided you, and you found very similar results. It allows doctors to consider however they feel is best to monitor for activity, whether vision, or imaging, or both. But if you use vision, perhaps you can be really sure by looking at two visits to know where that vision is.

DR. HAHN: That's a great point. Patients with pathologic myopia are often difficult to image. They have long axial lengths, they may have a deep staphyloma, or the quality of their OCT imaging may be a little grainy or difficult to capture. To definitively determine whether fluid is present, or whether there's some subretinal hyperreflectivity, which is often seen in patients with myopic choroidal neovascularization, is somewhat challenging.

Along the same lines, it can also be difficult to accurately assess subtle changes in vision in this population of patients, who often have quite good vision. In practice, I typically do a hybrid of the two. I assess retreatment criteria based on both vision and findings on OCT or angiography.

It is also my experience that patients with this condition are often very sensitive to their vision, and they are often very reliable indicators of whether there have been changes. Many patients will let me know there has been a change, and even if there are very subtle findings that I may not have definitively used to determine whether retreatment criteria were important, I will still often plan to reinject them, and I think that often prevents further recurrences.

DR. BRESSLER: That's very helpful. When we start anti-VEGF therapy in macular degeneration, a high percentage of patients still need treatment two years later, three years later, five years later. What did you see at one year in the RADIANCE study? Did you still have to consider treating a majority of those patients, or is it different from macular degeneration using anti-VEGF therapy?

DR. HAHN: That highlights our understanding of the difference in pathogenesis between macular degeneration and myopic choroidal neovascularization. Macular degeneration, for the most part, requires chronic therapy consistent with our understanding that this is a chronic disease.

In patients with myopic choroidal neovascularization, results from the RADIANCE trial corroborate our personal experiences, which suggest that it may be more self-limited. In the RADIANCE trial, in one of the subgroups receiving ranibizumab retreatment, 50% of patients only required one to two injections up front. Across the entire ranibizumab subgroups, more than 60% of patients did not require injections after month 6. This suggests that myopic CNV may be a limited disease that we need to quiet down up front and it may remain in remission after.

However, about 15% of patients required six to 12 injections, which suggests that myopic CNV may not be so cut and dried and a certain number of patients do have chronic disease and require further retreatment, which underscores our need to treat each patient on an individual basis.

DR. BRESSLER: So the lesson is, you will do far more limited injections on average, but don't rest because some people will need perhaps as many as your typical macular degeneration patients.

DR. HAHN: That's exactly right. And from personal experience, we all know that these patients can develop recurrences down the road. So I think all these patients do need frequent follow-up.

DR. BRESSLER: Now how about safety: were there any safety issues? We're dealing with an elongated eye, we're dealing with perhaps a thinner choroid. Did any safety issues come out of this, or are we fortunately still relatively safe with this therapy?

DR. HAHN: Fortunately we are still relatively safe. Ranibizumab, like many of the other anti-VEGF agents across the board, seems to be very well tolerated, and this trial corroborated that. There were no deaths or no endophthalmitis, and no safety events were identified. The safety profile was similar to that found in other studies.

DR. BRESSLER: Paul, thank you for joining us at this meeting of the American Society of Retina Specialists in Boston and for sharing with our audience here more detail on the information you presented on the RADIANCE trial.

DR. HAHN: It was my pleasure; thank you for having me.

DR. BRESSLER: Let's quickly summarize our discussion today in light of our learning objectives. The first learning objective was to describe research and development in the identification and treatment of myopic choroidal neovascularization. We learned from Dr. Paul Hahn at NJRetina that the radiance trial has given us definitive confidence

that treating myopic choroidal neovascularization with anti-VEGF therapy, in this case using ranibizumab, can be very beneficial for these patients and is probably the way to go.

Unlike macular degeneration studies, the RADIANCE trial seems to show us that fewer injections on average are needed, but still there will be patients who need numerous injections through one year.

The second learning objective was to describe how early diagnosis and treatment of macular degeneration can improve clinical outcomes. Dr. Colin Tan from Singapore shared with us information from the EVEREST II trial. In the EVEREST II trial, when patients presented with the polypoidal choroidal vasculopathy pattern of macular degeneration, we learned that if you combine ranibizumab with photodynamic therapy, you may get vision outcomes that are at least as good, if not somewhat better, than using ranibizumab alone from the start. This was shown to be very safe, and perhaps by combining these two therapies, you might even need fewer injections over time.

The third and final learning objective of this podcast was to identify patients who might be appropriate for getting anti-VEGF therapy treatments based on the available therapies and the latest data. Both Dr. Tan and Dr. Hahn have shared with us information that has helped us identify that patients with polypoidal choroidal vasculopathy, a specific pattern of choroidal neovascularization in macular degeneration, and also choroidal neovascularization from pathologic myopia, may benefit from anti-VEGF therapy as given in these trials. I think this has helped us move forward in managing and reducing vision loss and gaining vision from these conditions.

I want to thank both my guests, Dr. Paul Hahn from NJRetina and Dr. Colin Tan from the Duke National University of Singapore Medical School, for sharing their insights with us today.

DR. BRESSLER: I'm Dr. Neil Bressler from the Johns Hopkins University School of Medicine, and we'll be returning soon with our next *e*Ophthalmology podcast in December 2017, from the Asia Pacific Vitreoretinal Society, or the APVRS Congress, being held in Kuala Lumpur this year. Thank you all for joining us.

MR. BUSKER:
This podcast is presented in conjunction with *e*Ophthalmology Review, a peer-reviewed CME credit publication that is emailed monthly to clinicians treating patients with retinal diseases. This activity has been developed for ophthalmologists, retina specialists, and others involved in the care of patients with retina diseases.

There are no fees or prerequisites for this activity.
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education, through the joint sponsorship of the Johns Hopkins University School of Medicine.

The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians. The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 credit*(s)™. Physicians should claim only the credit commensurate with the extent of their participation in this activity. This educational resource is provided without charge, but registration is required. To register to receive *e*Ophthamology Review by email, please go to our website: www.eophthalmologyreview.org.

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of the names of the Johns Hopkins University School of Medicine implies review of educational format, design, and approach.

Please review the complete prescribing information for specific drugs, combinations of drugs, or use of medical equipment, including indication, contraindications, warnings, and adverse effects, before administering therapy to patients.

*e*Ophthalmology Review is supported by educational grants from Genentech, Inc., Regeneron Pharmaceuticals, Inc., and Carl Zeiss Meditec.
Thank you for listening.

CME/CE INFORMATION

ACCREDITATION STATEMENT
Physicians
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the Johns Hopkins University School of Medicine. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Physicians

The Johns Hopkins University School of Medicine designates this enduring material for a maximum of *0.5 AMA PRA Category 1 Credit*(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity

POLICY ON SPEAKER AND PROVIDER DISCLOSURE

It is the policy of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing that the speaker and provider globally disclose conflicts of interest. The Johns Hopkins University School of Medicine OCME has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Detailed disclosure will be made in the instructional materials.

INTERNET CME/CE POLICY

DISCLAIMER STATEMENT

STATEMENT OF RESPONSIBILITY

STATEMENT OF NEED

INTENDED AUDIENCE

CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY PARTICIPANTS

HARDWARE & SOFTWARE REQUIREMENTS

COMPLETE CME INFORMATION

This activity was developed in collaboration with DKBmed.