

Highlights from the Cannes Retina Festival: 24th Annual Meeting of ASRS & 6th Annual Meeting of EVRS

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BY RISHI P. SINGH, MD

STATEMENT OF NEED

The Cannes Retina Festival is an international meeting with globe-spanning reach. The sponsors said it was believed to be the largest number of people in the retinal field, from the most nations ever assembled, for a scientific retina conference. The meeting offered the opportunity for the advancement and diffusion of scientific knowledge.

The mission of the American Society of Retinal Specialists, the largest professional organization of vitreoretinal specialists in the world, is to provide a collegial open forum, to advance the understanding and treatment of vitreoretinal diseases and to enhance the ability of its members to provide the highest quality of patient care.

TARGET AUDIENCE

This activity is designed for retinal specialists.

LEARNING OBJECTIVES

Upon successful completion of this learning program, the participant should be able to:

- Identify and discuss notable guest lecturers from the Cannes Retina festival;
- Discuss 2-year results from the FOCUS trial;
- Identify the main outcomes of the PROTECT study;
- Cite the key factors of the RAVE trial; and
- Name some advances in vitreoretinal surgery for proliferative diabetic retinopathy.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions.

Participants have a choice of completing this activity online by visiting www.RetinaToday.com or by using the print forms following this activity.

Upon completing the activity and achieving a passing score of $\geq 70\%$ on the self-assessment test, participants will receive a CME credit letter awarding *AMA/PRA Category 1 Credit*[™] 4 weeks after the registration and evaluation materials are received. The estimated time to complete this activity is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and *RETINA TODAY*.

The Dulaney Foundation designates this educational activity for a maximum of 1 *AMA/PRA Category 1 Credit*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services that relate to the content of their presentation/material or the commercial contributors of this activity; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE DECLARATIONS

None.

FACULTY CREDENTIALS

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INTRODUCTION

The 24th Annual American Society of Retina Specialists (ASRS) Meeting, in conjunction with the 6th Annual European Vitreoretinal Society Meeting, was held in Cannes, France from September 9 to 13. The lectures and discussions ranged from advances in treatment of diabetic retinopathy, surgical innovations in vit-

reoretinal surgery and updates on the management of age-related macular degeneration (AMD). The featured guest speakers included Judah Folkman, MD, who spoke on the potential of future advances in ophthalmology from research in tumor angiogenesis, Brooks W. McCuen II, MD, who discussed evolving concepts in pharmacological vitreolysis, and Kirk H. Packo, MD, from Rush University Medical Center, who hypothesized on the future of vitrectomy technology. Dr. Packo is a member of the *RETINA TODAY* editorial board. This report highlights the noteworthy papers presented during the meeting as well as general consensus concepts that were discussed, as they shape the future practice patterns of vitreoretinal physicians.

NOTEWORTHY GUEST LECTURES

Judah Folkman, MD, Andrus Professor of Pediatric Surgery and Professor of Cell Biology at Harvard Medical School, delivered his lecture on the potential for future advances in ophthalmology from research in tumor angiogenesis. Widely considered the father of antiangiogenesis, Dr. Folkman was the first — in 1971 — to theorize that solid tumors are dependent on angiogenesis. His laboratory was the first to report a purified angiogenesis molecule, and his research has been translated in the treatment of cancer and non-neoplastic diseases. Based on recent studies of platelets, Dr. Folkman theorized that analysis of a patient's platelet angiogenesis proteome would be able to detect angiogenesis regulatory proteins released from human tumors $< 1\text{mm}^3$. This may be useful in detecting the occurrence of wet AMD months or years before conventional methods.

Brooks W. McCuen II, MD, delivered the Gertrude D. Pyron Award lecture on the evolving concepts in pharmacological vitreolysis.

The ASRS also recognized Brooks W. McCuen II, MD, for his outstanding achievement in retina research. Dr. McCuen is Duke University Eye Center's Robert Macheimer Professor of Ophthalmology, director of the vitreoretinal service and vice chairman of the department of ophthalmology. Dr. McCuen delivered the Gertrude D. Pyron Award lecture on the evolving concepts in pharmacological vitreolysis. He identified its potential uses that include vitreomacular

traction syndrome, idiopathic macular holes, myopic patients with attached posterior hyaloid and diabetic patients with adherent hyaloid. Dr. McCuen identified potential agents for pharmacologic vitreolysis and presented his animal data on the safety and efficacy of Dispase (ie, bacillus-derived neutral metalloprotease). In summary, pharmacological vitreolysis has the potential to make surgery simpler, safer and faster. It also enhances the potential of smaller gauge vitrectomy instruments and, in some cases, altogether obviate vitreous surgery.

• **Intravitreal ranibizumab (Lucentis; Genetech, San Francisco) plus verteporfin photodynamic therapy (PDT) for neovascular AMD: FOCUS 2-year results**

Andrew N. Antosyk, MD, presented 2-year results from the FOCUS study comparing the safety and efficacy of monthly intravitreal injections of ranibizumab in combination with verteporfin PDT (Visudyne; Novartis, Hanover, NJ) versus PDT alone in the treatment of predominately classic subfoveal choroidal neovascularization (CNV) due to AMD. The phase 1/2 study involved 105 ranibizumab and PDT patients and 56 sham- and PDT-treated patients. PDT was given 7 days before injection of either ranibizumab or sham. The primary outcome measurement for the study was the proportion of patients who at 24 months lost <15 letters from baseline BCVA.

A significant change was made to protocol during the course of the FOCUS study.

A significant change was made to the protocol during the course of the study. There were a greater number of patients who experienced transient uveitis after the injection of ranibizumab. Prior to the protocol amendment, PDT and ranibizumab had a higher rate of intraocular inflammation (13.3%) compared with after the amendment (2.9%). This was thought to be due to the lyophilized formulation used in the study and possibly due to the time interval between PDT and ranibizumab injection. The protocol was amended by increasing the time interval between PDT and ranibizumab injection to 28 days.

The combination of ranibizumab and PDT was safe and efficacious at year 2 in the FOCUS study.

Presumed endophthalmitis occurred in 5.7% of treated patients, which included both investigator reported endophthalmitis (n=3) and uveitis (n=3) cases. No overall imbalance of key arterial thromboembolic events was observed. The treatment effect of PDT and ranibizumab observed in year 1 was maintained through year 2, with 88% of subjects losing <15 letters and 25% of patients gaining >15 letters. This represented a cumulative 12.4-letter benefit in mean visual acuity change from baseline. Finally, fewer patients in the PDT and ranibizumab arm received additional PDT.

• **Open-label, multicenter, phase 2 study assessing the safety and efficacy of same-day verteporfin and liquid ranibizumab 0.5 mg (PROTECT Study)**

Sebastian Wolf, MD, discussed the 4-month results of the phase 2 study assessing efficacy and safety of combination therapy with PDT with ranibizumab for wet AMD. The study enrolled 32 patients with subfoveal predominately classic or occult lesions only. Patients received ranibizumab injections at baseline, months 1, 2 and 3 and received verteporfin PDT at baseline and if deemed necessary by the study investigator at months 3, 6 and 9. The primary endpoint of this study was to determine the incidence of severe vision loss (≥ 30 letter loss within 14 days of combination treatment and persisting for ≥ 14 days).

No patients experienced severe visual loss during the course of treatment, and only one patient experienced moderate visual loss (>15-letter decline). A negligible amount of ocular and nonocular side effects occurred during the study. A 6.9-letter mean improvement over baseline vision was seen. The authors concluded that verteporfin PDT can be safely combined with intravitreal ranibizumab on the same day. Same-day combination therapy resulted in a significant reduction of central retinal thickness and leakage, and the approach may result in increased benefit (eg, rate of visual improvement, decrease the need for retreatment). The clinical trial will run for 9 months.

• **Intravitreally injected anti-vascular endothelial growth factor (VEGF) drugs exert a biological effect in the fellow eye**

Tongalp H. Tezel, MD, presented a study investigating the fellow eye effects after intravitreal injection of anti-VEGF drugs in the management of bilateral exudative AMD. In his prospective case series, patients received bevacizumab (Avastin; Genetech,

San Francisco), pegaptanib sodium (Macugen; OSI/Eyeteck and Pfizer, New York, NY), or the combination of bevacizumab and triamcinolone (Kenalog). Pegaptanib exerted the most effect on the fellow eye within the study followed by bevacizumab and bevacizumab plus triamcinolone. Dr. Tezel concluded that intravitreal injections of anti-VEGF agents exert a biologic effect in the fellow eye, possible via systemic absorption. Given this data, long-term intravitreal injections of these drugs merits extreme caution due to their possible interference with physiological angiogenesis, such as coronary vessel collateral formation and wound healing.

Sutureless closure seen with 23- and 25-gauge systems were virtually equivalent when angled incisions were used in the 23-gauge system.

• Pharmacokinetics of intravitreal bevacizumab

Sophie J. Bakri, MD, discussed studies on the pharmacokinetics of 1.25 mg intravitreal bevacizumab in an animal model. The purpose of the study was to evaluate the systemic exposure seen with intravitreal dosing of this drug. At days 1, 3, 8, 15 and 29 after intravitreal injection, blood samples were assayed for bevacizumab. The half-life was 4.32 days in the vitreous, 4.88 days in the aqueous humor and 6.86 days in the serum. The time to reach maximum concentration was 1 day in the vitreous, 3 days in the aqueous humor and 8 days in the serum. Systemic exposure of bevacizumab was found to be 1.7% of vitreous exposure, and a measurable fellow eye affect was also seen. Dr. Bakri concluded that a negligible amount of bevacizumab exposure is seen systemically after intravitreal injection, and future studies evaluating ranibizumab are planned.

• Triple combination therapy for treatment of CNV membranes due to AMD

Albert J. Augustin, MD, presented a pilot study on the use of triple therapy for CNV due to AMD. Many recent studies have highlighted the decreased treatments and improved visual outcome after the combination of PDT and intravitreal triamcinolone. In this pilot study, 58 patients were enrolled to receive PDT therapy at 80% fluence, 1.25 mg of intravitreal bevacizumab at the time of PDT, and 800 µg dexametha-

sone 18 hours after the initial treatments. All lesion types were included in the study, and mean follow-up was 30 weeks. A monoport core vitrectomy was performed in a small number of patients to facilitate drug implantation. After triple treatment, patients experienced an average of 1.9 lines of visual improvement and a mean decrease of 184 µm. No angiographic evidence of leakage occurred after triple therapy in any patient in the study. In summary, triple therapy resulted in a significant visual increase with no required retreatment with PDT. Future larger randomized clinical trials would be helpful in determining what lesions benefit most from triple therapy management.

• Integrity of wound closure after 23-gauge versus 25-gauge sutureless vitrectomy

Oswaldo F.M. Brasil, MD, presented study results from the evaluation of 23-gauge versus 25-gauge sutureless vitrectomy systems using either angled or straight incisions in an animal model. Alcon (Fort Worth, Texas) 23- and 25-gauge vitrectomies were performed on rabbits with either incision technique, and wound leakage was evaluated by examining the eyes for physiological leakage seen with the presence of trypan blue and evaluating histological closure of the wound. Straight incisions showed physiological leakage in 10.3% of rabbits 1 day after surgery versus 5.3% of angled incisions for the same time. The 23- and 25-gauge systems had equal and small percentage of rabbits with physiological leakage (4.4% for both). Histological closure favored angled incisions over straight incision, and there was no statistical difference in closure seen between 23-gauge angled and both 25-gauge straight and 25-gauge angled incisions. The authors concluded that the sutureless closure seen with 23- and 25-gauge systems were virtually equivalent when angled incisions were used in the 23-gauge system.

• Ranibizumab in ischemic central retinal vein occlusion (CRVO): Interim optical coherence tomography (OCT) and visual results from the RAVE trial

Matthew S. Benz, MD, presented the phase 1 open-label study of the use of ranibizumab in the management of ischemic CRVO. Patients enrolled in the study received 9 monthly intravitreal injections of 0.5 mg ranibizumab. The primary outcome of the study is the need for panretinal photocoagulation, and secondary outcome measurements were final vision and changes of central macular thickness by OCT. Five

patients have enrolled within the trial thus far. Baseline visual acuity at 2 months follow-up improved from 20/500 to 20/400. Mean central macular thickness improved from 304 μm initially to 172 μm . No patient developed anterior segment neovascularization, and no patient needed panretinal photocoagulation. The authors predict that the study's long-term results will be as favorable as the short-term results.

• **Predictive factors for visual outcome after intravitreal triamcinolone acetonide injection for diabetic macular edema (DME)**

I presented a study on the predictive factors seen by OCT prior to the injection of intravitreal triamcinolone for the management of DME. In this retrospective review, 52 eyes of 42 patients with clinically significant macular edema were administered 4 mg intravitreal triamcinolone. Preinjection OCTs were scored for the type of DME seen (ie, cystoid, diffuse thickening, subretinal fluid, posterior hyaloidal traction), and for the presence of an epiretinal membrane (ERM). Multivariate linear regression analysis demonstrated that worse baseline vision and the presence of cystoid macular edema and subretinal fluid on the initial OCT correlated with a positive visual outcome at the end of the 3-month study. The presence of an ERM conferred a negative outcome on final vision, with many cases exhibiting a worse visual outcome than the preinjection vision. The authors concluded that the OCT characteristics and baseline vision were useful predictors for success of intravitreal triamcinolone for DME. Furthermore, the presence of an ERM on the initial OCT should be a relative contraindication to using intravitreal triamcinolone for DME.

• **Injection of intravitreal bevacizumab before vitrectomy in the treatment of severe proliferative diabetic retinopathy (PDR)**

Stanislao Rizzo, MD, presented data from his study on the use of bevacizumab prior to pars plana vitrectomy for PDR. Twenty-two patients with severe PDR underwent pars plana vitrectomy for tractional retinal detachments, combined tractional and rhegmatogenous detachments and vitreous hemorrhage. Surgical time, intraoperative bleeding time and the need for bimanual membrane dissection and relaxing retinotomies were recorded. Patients with bevacizumab prior to surgery had a mean surgical time of 57 minutes versus 83 minutes in those patients without prior bevacizumab. Ten episodes of intraopera-

tive bleeding were observed in the untreated group in comparison with two in the treated group. No complications from the use of intravitreal bevacizumab were seen during the study. The authors concluded that bevacizumab allowed for a shorter, easier and safer pars plana vitrectomy in the management of surgical PDR.

OCT characteristics and baseline vision were useful predictors for success of intravitreal triamcinolone for DME.

• **Advances in vitreoretinal surgery for proliferative diabetic retinopathy**

Robert Avery, MD, reported on the use of bevacizumab for PDR. He identified potential roles for bevacizumab in treating rubeosis, persistent neovascularization despite panretinal photocoagulation, vitreous hemorrhage precluding panretinal photocoagulation, PDR with DME and before vitrectomy for PDR as it may reduce bleeding when fibrovascular tissue is cut. Dr. Avery has found a benefit in using bevacizumab 1 week prior to diabetic retinal traction detachment surgery, in that qualitatively he has noticed less active bleeding during surgery and regression of neovascular vessels facilitating surgery. He noted, however, that there was no quantitative measurement to show its efficacy. Dr. Avery reported the findings of bevacizumab use in 45 eyes (32 patients) for PDR. The mean follow-up was only 5 weeks. Intravitreal bevacizumab doses of 6.2 μg to 1.25 mg caused cessation of leakage from the neovascular tissue assessed by fluorescein angiography in many patients within the first week of the study.

Within 2 weeks of treatment, however, a small number of patients began to show recurrent neovascular leakage. A fellow eye effect was observed in patients treated with 1.25 mg of bevacizumab, including regression of retinal neovascularization, decreased angiographic leakage and regression of iris neovascularization. This finding suggests systemic absorption of the drug — therefore, lower bevacizumab doses may be required to avoid the fellow eye effect. Dr. Avery concluded that bevacizumab may be a useful adjunctive agent in the management of PDR, but caution should be taken since long-term safety information is unknown at this time, and fellow eye effects suggest possible systemic exposure. ■

CME QUESTIONS

Circle the most appropriate answer in the "ANSWER SECTION" on the following page.

1. According to the activity, who is widely considered the father of antiangiogenesis?
 - a. Judah Folkman, MD
 - b. Brooks W. McCuen II, MD
 - c. Tongalp H. Tezel, MD
 - d. Matthew S. Benz, MD
2. According to the Gertrude D. Pyron Award lecture, which of the following is not a potential use for pharmacological vitreolysis?
 - a. vitreomacular traction syndrome
 - b. idiopathic macular holes
 - c. retinal detachment
 - d. attached posterior hyloid and adherent hyloid
3. Which of the following statements is true with regard to the 2-year results from the FOCUS study?
 - a. Patients were treated with ranibizumab plus verteporfin PDT
 - b. There was a significant change made to protocol during the course of the study
 - c. The combination treatment was safe and efficacious
 - d. all of the above
4. In the PROTECT study, no patients experienced severe visual loss during the course of treatment.
 - a. True
 - b. False
5. What did the data show with regard to the biological effect in the fellow eye or intravitreally injected anti-VEGF drugs?
 - a. The agents had no effect on the fellow eye
 - b. The agents may interfere with physiological angiogenesis
 - c. The agents caused AMD to develop in the fellow eye
 - d. The agents cured AMD in the fellow eye
6. What is the triple combination therapy for the treatment of CNV in the presentation by Albert J. Augustin, MD?
 - a. pegaptanib, ranibizumab and bevacizumab
 - b. PDT, dexamethasone and pegaptanib
 - c. PDT, intravitreal ranibizumab and dexamethasone
 - d. PDT, intravitreal bevacizumab and dexamethasone
7. Were the short-term results from the RAVE trial favorable?
 - a. Yes
 - b. No
8. What did two authors find with respect to bevacizumab use in severe PDR?
 - a. Surgical time in patients taking the agent was decreased
 - b. Pars plana vitrectomy was easier and safer with the agent
 - c. The agent may be a useful adjunct in the management of PDR
 - d. All of the above

REGISTRATION/EVALUATION FORM: HIGHLIGHTS FROM THE CANNES RETINA FESTIVAL

To obtain AMA/PRA category 1 credit, you must:

- Read the learning objectives and the CME article and complete the self-assessment test.
- Photocopy and complete this registration/evaluation form and record your test answers in the Answer Section below.
- Send the Registration/Evaluation form to **The Dulaney Foundation, PO Box 44408, Phoenix, AZ 85064, or fax to 602-508-4893.**
- Retain a copy of your test answers. Your answer sheet will be graded, and if you achieve a passing score of 70% or better, you will receive a CME credit letter awarding AMA/PRA category 1 credit within 4 weeks. If you do not achieve a passing score, you will be notified and offered the opportunity to complete the activity again.

ANSWER SECTION

Circle the best answer for each question on page 46.

1. A B C D 2. A B C D 3. A B C D 4. A B
5. A B C D 6. A B C D 7. A B 8. A B C D

REGISTRATION FORM

First name _____ Last name _____ Degree (MD, PhD) _____

Specialty _____

Institution or practice name _____

Address _____

City _____ State _____ Zip Code _____ Country _____

Telephone _____ Fax _____ E-mail address _____

The processing fee has been underwritten by an educational grant from Eli Lilly and Company.

I attest that I have completed this activity as designed and I am claiming _____ (up to 1 credit) AMA/PRA category 1 credit.

Signature _____ Date _____

Credit for this activity is available until November 30, 2007.

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. Please assist us in evaluating the effectiveness of this activity and make recommendations for future educational offerings by completing this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters and long-term credit retention information will only be issued upon receipt of this completed evaluation. Thank you for your cooperation.

OBJECTIVES

After successful completion of this program, you should be able to:

- | | | | | | |
|---|---|---|---|---|---|
| • Identify and discuss notable guest lectures from the Cannes Retina Festival; | 5 | 4 | 3 | 2 | 1 |
| • Discuss 2-year results from the FOCUS trial; | 5 | 4 | 3 | 2 | 1 |
| • Identify the main outcomes of the PROTECT STUDY; | 5 | 4 | 3 | 2 | 1 |
| • Cite the key factors of the RAVE trial; and | 5 | 4 | 3 | 2 | 1 |
| • Name some advances in vitreoretinal surgery for proliferative diabetic retinopathy. | 5 | 4 | 3 | 2 | 1 |

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

OVERALL EVALUATION

- | | | | | | |
|--|---|---|---|---|---|
| • The information presented increased my awareness/understanding of the subject. | 5 | 4 | 3 | 2 | 1 |
| • The information presented will influence how I practice. | 5 | 4 | 3 | 2 | 1 |
| • The information presented will help me improve patient care. | 5 | 4 | 3 | 2 | 1 |
| • The faculty demonstrated current knowledge of the subject. | 5 | 4 | 3 | 2 | 1 |
| • The program was educationally sound and scientifically balanced. | 5 | 4 | 3 | 2 | 1 |
| • The program avoided commercial bias or influence. | 5 | 4 | 3 | 2 | 1 |
| • Overall, the program met my expectations. | 5 | 4 | 3 | 2 | 1 |
| • I would recommend this program to my colleagues. | 5 | 4 | 3 | 2 | 1 |

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

- If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so: _____
- Please provide any additional comments pertaining to this activity (positive and negative) and suggestions for improvements: _____