Retinal PHYSICIAN

Article

Retinal Physician Symposium Covers Broad Range of Topics

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feature

Retinal Physician Symposium Covers Broad Range of Topics

Top specialists provide insights on timely issues.

COMPILED BY THE RETINAL PHYSICIAN EDITORIAL STAFF

Many of the country's leading retina specialists gathered at the Atlantis resort on Paradise Island in the Bahamas from May 31 to June 3 for the Second Annual *Retinal Physician* Symposium (RPS). The theme of this year's meeting was Current Concepts in Retinal Medicine. The meeting generated considerable excitement as Genentech chose the RPS to release the first results of the key PIER trial evaluating quarterly dosing for ranibizumab (Lucentis) in treating wet age-related macular degeneration (AMD).

The following are condensed recaps of key presentations that took place during the 4 days of the Symposium.

WET AMD TREATMENTS

Ranibizumab (Lucentis)

A key focus of this year's RPS was the ongoing assessment of ranibizumab (Lucentis, Genentech). Interest was generated by 2 key events: the release of 1-year data from the PIER trial and the expectation that ranibizumab would be approved by the Food and Drug Administration shortly after the Symposium concluded. Indeed, ranibizumab was approved on June 30 as a treatment for wet AMD.

Peter Kaiser, MD, provided a recap of the key clinical trials for ranibizumab, including the 2 pivotal phase 3 studies, MARINA and ANCHOR. He also noted other, more narrowly focused studies of ranibizumab such as SAILOR, FOCUS, and PrONTO. (*Retinal Physician* has previously reported on

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these studies.)

Based on the already completed key studies, Dr. Kaiser concluded that Lucentis has shown itself to be an efficacious drug with an excellent safety profile. He noted that the range of adverse events seen in ranibizumab trials "were really limited to things that we've come to expect with intravitreal injections."

David Brown, MD, provided new information when he announced the 1-year results of the PIER study, which was primarily designed to determine whether ranibizumab could be injected quarterly rather than monthly (after 3
initial monthly injections) and maintain its effectiveness.

Dr. Brown reported that the PIER study showed ranibizumab to be a safe drug. However, while quarterly dosing on average provided a 15- to 16-letter improvement over sham injections, the visual acuity of patients receiving quarterly injections of ranibizumab had on average returned to baseline by month 12.

The PIER data have led Genentech to recommend that patients receive either monthly injections of ranibizumab, or have their retreatment schedules determined through individualized testing.

Bevacizumab (Avastin)

The update on bevacizumab (Avastin, Genentech) was presented by Philip Rosenfeld, MD, PhD, who pioneered the use of bevacizumab as an off-label therapy for the treatment of wet AMD.

Dr. Rosenfeld described how he had initially recognized the molecular similarities between ranibizumab and bevacizumab and determined that bevacizumab might be an effective treatment for wet AMD. He began with intravenous delivery of bevacizumab to a few wet AMD patients.

Dr. Rosenfeld said he was well aware of systemic side effects that occurred with some cancer patients treated with bevacizumab, though he did not see those side effects in his AMD patients. However, he wanted to avoid the potential risk of systemic side effects and switched to intravitreal injection as the delivery method for bevacizumab.

Dr. Rosenfeld reported on a patient who did not respond to photodynamic therapy (PDT), triamcinolone acetonide (Kenalog, Bristol-Myers Squibb), or pegaptanib sodium (Macugen, OSI), but who demonstrated significant and long-lasting visual improvement after just 1 injection of 1.25 mg of bevacizumab.

In terms of safety, he noted that short-term data on 7000 bevacizumab injections raised no major safety concerns.

"No apparent safety signals were identified," he reported.

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Dr. Rosenfeld concluded his presentation by saying that retina specialists should not feel guilty about using bevacizumab as a treatment for wet AMD.

"It's legal, and it's ethical if you're using good clinical judgment," he asserted. "Obviously, we do need prospective clinical trials."

Other Pharmacotherapies

Peter Kaiser, MD, discussed several potential but lesser-known wet AMD therapies that are currently in clinical trials — vascular endothelial growth factor (VEGF) Trap (Regeneron), RNA interference (being developed by both Acuity Pharmaceuticals and Sirna Therapeutics), and squalamine (Evizon, Genaera).

Dr. Kaiser finds VEGF Trap particularly interesting because in creating a decoy receptor for VEGF, it binds well to all forms of VEGF and remains effective at low concentrations, possibly offering a longer-lasting duration of action.

Following a promising 6-week, 21-patient phase 1 trial during which the median improvement in visual acuity was 13 letters, Regeneron has initiated a larger phase 2 trial to determine safety and efficacy at doses up to 4 mg.

The mechanism of action of RNA interference is to silence VEGF-producing genes through the injection of a form of double-stranded RNA. Sirna has completed a promising 26-patient, phase 1 trial that consisted of 1 injection. The Sirna compound, which acts against the VEGF receptor, demonstrated improved or stabilized vision in 96% of the study population, with 23% of patients showing a 3 line vision gain at 8 weeks. Sirna is now forming a phase 2 trial.

Acuity has conducted a 15-patient, 2 injection phase 1 trial with its Cand5 compound, which attacks VEGF directly. In this study, 80% of patients demonstrated stable or improved vision. Dr. Kaiser reported that the safety profile of Cand5 proved to be excellent in this trial. A phase 2 trial is currently nearing completion.

Dr. Kaiser briefly mentioned squalamine, an antiangiogenic that is given intravenously and that showed some ability to stabilize vision in phase 2 trials. A new, dose-escalating trial of squalamine has now been initiated.

PDT and Intravitreal Steroids

Albert Augustin, MD, reported on an interesting combination called "triple therapy" in which the patient is treated with an anti-inflammatory steroid, bevacizumab, and modified PDT with a lower light dose.

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Dr. Augustin said that in 1 series of 64 eyes, 7 patients who received triple therapy all showed significant improvement in visual acuity in just 1 treatment cycle. A second bevacizumab injection was performed in only 7 eyes.

"We believe this is a more finite treatment," said Dr. Augustin. "It's more a cure vs a suppression of the disease process. Up to now, we haven't seen any steroid-related or other severe side effects of the treatment."

The PrONTO Study

Dr. Rosenfeld had the idea which led to the PrONTO study after treating several patients with ranibizumab who did not require additional retreatment for as long as 31 months. In fact, their vision continued to improve without retreatment. He determined that patients responded differently to this therapy and that retreatment could be determined on an individual basis.

Dr. Rosenfeld reasoned that vision loss was gradual as the fluid accumulated and that optical coherence tomography (OCT) was reliable in detecting the fluid before it became symptomatic. Initially, all patients in the study received 3 monthly injections. They received additional injections only if the OCT measurements showed a need for retreatment.

"Our questions were: how quickly does the OCT improve once we start injecting? How quickly does the visual acuity improve? And can these visual acuity improvements be maintained 2 years if we use this prn regimen?"

The criteria for retreatment as measured by OCT were essentially one or more of the following: loss of at least 5 letters of vision, evidence of fluid, increase in central retinal thickness, new hemorrhage, and/or new evidence of classic choroidal neovascularization (CNV).

Using these criteria, the mean number of injections per patient in year 1 of a 2-year 40-patient study was 5.5, though at least 1 patient received 13 injections. Clearly, the need for re-injection is unpredictable and varies from individual to individual. The PrONTO study offers one way to determine individual retreatment schedules.

OCT Assessments of Lucentis

Dr. Brown reported on quantitative vs qualitative OCT assessments of disease progression following treatment with ranibizumab.

He noted that 4 different types of edema routinely return following treatment with ranibizumab. These are diffuse edema, intraretinal cysts, subretinal edema, and subretinal pigment epithelium fluid.

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"A patient has anti-VEGF therapy and gets a nice response," noted Dr. Brown. "With time, after treatment, you get diffuse edema. In other words, there's a thickening but no bubbles. This will only be shown by quantitative OCT if it accurately measures the retinal boundaries."

Dr. Brown reports that in performing quantitative OCT assessments following anti-VEGF treatments, the error rate in identifying the need for retreatment can be as high as 70%. This is because the computer is prone to fixation errors, has difficulty in finding retinal boundaries, and fails to note the presence of subretinal pigment epithelium fluid.

With qualitative OCT assessment, the presence of fluid is visible and easy to detect. When fluid is detected, it is recommended that the retina specialist initiate retreatment.

"As Phil (Rosenfeld) says, he treats when he sees fluid," noted Dr. Brown.

High-Resolution SLO/OCT: The Future

Dr. Rosenfeld reported on the anticipated arrival of "next-generation" OCT technology, which is called spectral domain and is currently being developed by several competing companies, including Carl Zeiss Meditec (Dublin, Calif) and Topcon (Paramus, NJ). Dr. Rosenfeld predicts that one or more of these systems will be commercially available within the next year.

The advantages of spectral domain include increased speed, no moving parts, and 2000 detector elements that generate 29000 lines per second compared to 400 lines per second for today's OCT-3. The result is better sensitivity, higher resolution, and 3-D imaging.

"So, we are going to have higher resolution. It's going to be faster and you are going to be able to reconstruct images. You're going to be able to precisely place where the pathology is in the different layers of the retina based on the vascular landmarks of the fundus image. You are going to be able to do a lot of neat things because you will have this huge database that can be manipulated any way you want," concluded Dr. Rosenfeld.

SURGERY

Surgery for AMD: Is It Dead?

Paul Tornambe, MD, says he never felt that surgery was alive for AMD. Dr. Tornambe says, "Any disease where you treat the effect of the stimulus rather than treating the stimulus is not going to be successful." He says "that until we are able to do something directly with the up-regulation of a VEGF gene, that as long as VEGF keeps getting produced, we're going to have to keep retreating these people." Dr. Tornambe believes that something has to occur further upstream to be effective.

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He also believes choroidal neovascular membrane (CNVM) removal is "dead" and that the Submacular Surgery Trials (SST) showed really no visual benefit. Dr. Tornambe is disappointed with the results in dealing with large clots. He thinks that the intravitreal injection of dexamethasone and bevacizumab or ranibizumab is exciting and that drugs will minimize the damage that is ultimately done.

"Ninety-five percent of the macula operations we perform now will not be performed in 5 years, but I think we're very innovative, and we certainly try everything once," says Dr. Tornambe.

PREVENTION OF AMD

AMD: Genetics and Nutrition

Darius Moshfeghi, MD, stated in his Nutrition, AREDS, AREDS II presentation that the AREDS trial, "has demonstrated the feasibility and efficacy of antioxidant plus zinc supplementation in preventing progression to advanced forms of AMD in patients with intermediate and advanced forms of AMD."

In addition, Dr. Moshfeghi said the AREDS formulation resulted in positive visual acuity outcomes relative to placebo. Lastly, the AREDS II trial is enrolling patients to determine the additional benefit, if any, of xanthophyll and/or omega-3 long-chain polyunsaturated fatty acid supplementation in prevention of progression of AMD.

Cataract Surgery and Development of Advanced AMD

Susan Bressler, MD, gave a presentation on the effect of cataract surgery on the development of neovascular AMD. Dr. Bressler stated that multiple analytic approaches on a large, well-categorized cohort (AREDS) provides no clear evidence of an adverse association between cataract surgery and development of neovascular AMD and that AMD patients in need of cataract surgery can probably be reassured of little to no increased risk of CNV due to surgery.

Prevention of Advanced AMD

During his talk on risk factors for choroidal neovascularization and AMD prevention trials, Allen C. Ho, MD, spoke about the exciting opportunities and developments with ranibizumab for patients with wet AMD. Dr. Ho covered prevention trials and the status of trials outside of AREDS — laser to drusen, rheopheresis, and the anecortave acetate trial. He said that lutein and zeoxanthine are going to be explored in the AREDS II trial. In addition, Dr. Ho is interested in docosahexaenoic acid (DHA) and elco-
sapentanoic acid and said that omega-3 fatty acids are thought to be protective. He believes that the positive effects of DHA are very suggestive and compelling.

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Dr. Ho is interested in laser to drusen. He likes the notion of trying to modify the thickened Bruch's membrane that might be a stimulus for choroidal neovascularization or atrophic AMD, however, preliminary studies did not support laser to drusen outside the confines of a clinical trial. He thinks that rheotherapy is a very interesting concept but noted that the MIRA-1 phase 3 trial of rheopheresis did not meet the primary efficacy outcome; another phase 3 trial is in planning stages because the initial study may have had significant and real confounder variables. He highlighted the anecortave acetate study, which is a pharmacologic prevention trial. He believes the drug to be most apt for prevention of choroidal neovascularization and may be a useful adjunct to Lucentis in the treatment of existing CNV.

OCULAR TUMORS

Experimental Therapies

Timothy Murray, MD, reported some promising results in animal studies for microvascular targeting, which combines pharmacological therapies for the treatment of retinoblastoma. "Combining anecortave acetate (Retaane, Alcon) and carboplatin essentially reduces tumor size and has the potential to eradicate tumor," explained Dr. Murray. He noted the potential of such a therapy depends on its dosage and delivery schedule.

DIABETIC MACULAR EDEMA

Pegaptanib Sodium (Macugen)

Christine Gonzales, MD, spoke about the phase 2 trial evaluating pegaptanib sodium for diabetic macular edema (DME). This study was designed to explore the safety and efficacy of the drug through week 36 for patients given pegaptanib every 6 weeks for up to 36 weeks.

Patients were randomized 1:1:1 into 3 different doses of pegaptanib or sham injection. Physicians had to feel comfortable deferring focal laser treatment for up to 16 weeks.

Dr. Gonzales reported a treatment effect as early as 6 weeks and a significant difference between the sham group and the pegaptanib group at
36 weeks. "Subjects that were assigned to Macugen in the phase 2 trial had better visual acuities," reported Dr. Gonzales. "They were more likely to show a reduction in the center thickness, and less likely to need focal laser when compared to the sham group."

Ranibizumab (Lucentis)

Quan Dong Nguyen, MD, presented the 1-year interim results of the Ranibizumab for Edema of the MAcula in Diabetes (READ) study. In this READ phase 1 trial, intravitreal ranibizumab was safe and tolerable at multiple injections for patients who have DME that has been refractory to laser photocoagulation or intravitreal injections of triamcinolone. No ocular or systemic side effects and no inflammation had been observed with repeated dosages of 0.5 mg of ranibizumab.

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"The primary outcome of the READ study, beyond safety, was change in foveal thickness between baseline and 7 months and the secondary outcome measures were changes from baseline in visual acuity and macular volume," explained Dr. Nguyen. Dr. Nguyen reported that at 7 months, (1 month after the fifth injection), the mean foveal thickness was 257 µm, a reduction of 246 µm (85% of the excess foveal thickness present at baseline; *P*=.005). The macular volume was 7.47 mm^3, a reduction of 1.75 mm^3, (77% of the excess macular volume at baseline; *P*=.009). "In addition," said Dr. Nguyen, "at month 7, we observed a mean visual acuity of 40.4 letters (20/40), an improvement of 12.3 letters (*P*=.005)."

Ruboxystaurin

Dr. Kaiser presented results from the Diabetic Retinopathy Studies (DRS)-1 and 2 for this drug. He reported that protein kinase C beta inhibitor (Ruboxistaurin, Eli Lilly) showed it could reduce the risk of sustained, moderate vision loss over a 3-year time period in patients with moderate, severe, to very severe non-proliferative DR disease.

"In addition, the drug was able to improve the number of patients with visual gain, specifically 3-line gainers with less decrease from baseline visual acuity in those patients receiving the drug," explained Dr. Kaiser. He concluded by saying the drug was being reviewed by the FDA.

PROLIFERATIVE DIABETIC RETINOPATHY

Vitrase, Plasmin

Dr. Kuppermann discussed studies on these 2 drugs as agents for pharmacologic vitreolysis. Vitrase (purified ovine lyophilized hyaluronidase, ISTA Pharmaceuticals) completed 2 large phase 3 studies assessing its safety and efficacy for clearance of vitreous hemorrhage, but the 2 pivotal studies did not result in the drug being approved for that indication. "While Vitrase showed a clinical benefit in clearing vitreous hemorrhage in some eyes, the data did not show statistical significance in its 2 individual trials for a variety of complex reasons," explained Dr. Kuppermann.

Vitrase is currently approved as a spreading agent for retrobulbar use, and is available as an off-label agent for intravitreal use. Dr. Kuppermann also discussed the use of Vitrase to induce a posterior vitreous detachment in patients with moderately severe non-proliferative diabetic retinopathy (PDR) in order to decrease the risk of progression to proliferative diabetic retinopathy. However, to date, only a pilot trial for this indication has been conducted with Vitrase.

Dr. Kuppermann also discussed the potential role of another agent for enzymatic vitreolysis, plasmin. He reported that 3 types of plasmin were in various stages of development — autologous plasmin, pooled plasmin, and microplasmin. Autologous plasmin is difficult to develop as a commercial product because it entails using an affinity cartridge to extract the plasmin from the patients' blood. Dr. Kuppermann saw either pooled plasmin (Bausch & Lomb) or microplasmin (ThromboGenics) as the

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more likely plasmin-based future of therapeutic agents. Dr. Kuppermann explained that pooled plasmin and microplasmin are being studied as surgical adjuvants for vitrectomy surgery in ongoing trials, and other indications are being explored as well.

He also pointed out some other possible indications for both drugs. "Future potential uses include the possibility of using vitreolytic agents such as Vitrase and plasmin for floaters, as well as modifying or enhancing the efficacy of other ophthalmic drugs," said Dr. Kuppermann.

Bevacizumab (Avastin)

Robert Avery, MD, discussed his off-label use of bevacizumab for patients with PDR. He found the therapy to be useful in an adjunctive role because of its ability to treat patients who cannot be fully treated with panretinal photocoagulation or patients with DME and severe PDR. Dr. Avery explained that bevacizumab was helpful for DME and PDR patients in preventing exacerbation of their edema. He pointed out that the drug's efficacy and safety profile were promising as well.

"It works at very low doses, and that may be in part because it doesn't have to penetrate the retina to get where the disease is," stated Dr. Avery. "The vessels in diabetes are on the surface of the retina, and are on the iris, so there's no retinal penetration concern." He concluded by saying prospective trials were needed, but he was "excited" to have another PDR treatment tool.

PEDIATRIC RETINA
FEVR and ROP

Michael Trese, MD, presented on the pharmacologic management if pediatric retinal vascular disease, specifically on the use of pegaptinib sodium for blocking VEGF in familial exudative vitreoretinopathy (FEVR) and retinopathy of prematurity (ROP). Dr. Trese reported that in his experience, pegaptanib sodium reduces subretinal exudates in FEVR with repeat injection infrequently required. However, there is evidence showing that preretinal neovascularization is less responsive to therapy. In the treatment of ROP, pegaptanib sodium appears not to be as effective for rescue therapy as originally thought, However, Dr. Trese said that anti-VEGF therapy may be relative to the involution of tractional detachment cells and the hyaloid and tunica vasculosa lentis, so earlier therapy with pegaptanib sodium may have a favorable effect for ROP as an alternative to laser therapy, which destructs two-thirds of the retina.

"We do think that further study is needed to look at both — maybe selective, but also non-selective blockage of VEGF-A, to see if that's something which will improve our outcomes," said Dr. Trese.

RETINAL VASCULAR DISEASE
RVO and SCORE

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In her discussion on the NEI-sponsored SCORE study, Sharon Fekrat, MD, FACS, reviewed the 2005 Preferences and Trends (PAT) survey results on how retinal specialists treat retinal venous occlusive diseases (RVO), with the results being widely spread between grid pattern laser photocoagulation, intravitreal triamcinolone injection, and a combination of both approaches, among others. The SCORE study's goal is to assess the risks and the benefits of these 2 widely used therapies for RVO. Dr. Fekrat discussed several cases where triamcinolone has shown promise and outlined the SCORE protocol and its entry criteria. The SCORE study may indeed answer many unanswered questions about the use of intravitreal triamcinolone in eyes with RVO, she concluded.

Bevacizumab for Retinal Vascular Disease

Dr. Rosenfeld reported several cases where bevacizumab was used to treat retinal vascular disease with positive outcomes. Many of the cases presented were patients who had undergone previous therapy with intravitreal triamcinolone. Some of the patients responded well to triamcinolone but, because of IOP rises, required alternative therapy. Not all the patients did well on bevacizumab due to fluid persistence, and not all patients experienced visual acuity improvement that correlated with the anatomic improvement after bevacizumab injections. Of the treatment option for retinal vascular disease, Dr. Rosenfeld said, " We have limited data available. The duration of effect is quite unpredictable, and usually, multiple injections are necessary."

He added that he would still consider triamcinolone therapy better for patients with risks associated with glaucoma and cataracts, as well as those for whom frequent injections present a problem or for those who show fluid persistence despite monthly injections with bevacizumab.

Editor's Note: *Expanded coverage of the presentations from the Second Annual RPS will be published in a special edition of Retinal Physician, coming this November.*

Please join us next year for Retinal Physician Symposium 2007, April 12-15, 2007 at Sanibel Harbour Resort in Fort Myers, Fla. The Resort boasts all-new luxurious accommodations embodying the essence of seaside grandeur. Please contact Heather Seasholtz, director of the Conference Group at 215-643-8073 with any questions about the meeting.

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