First Anniversary Edition

EyeQ Report™

Ophthalmic Business Intelligence

Number 9 November 22, 2006

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EyeQ Report is a periodic newsletter highlighting information and events of importance to eye care practitioners, companies and investors

Published by:
Lachman Consulting LLC
www.lachmanconsulting.com

Written by Michael Lachman, unless otherwise noted

www.EyeQReport.com

AAO 2006: What Happened in Vegas...

Last week, the American Academy of Ophthalmology (AAO) and Asia Pacific Academy of Ophthalmology (APAO) hosted their joint meeting in fabulous Las Vegas, where it takes about 20 minutes to walk across the street for a meeting and about 2-3 times that long to catch a cab. Vegas is a big draw, particularly for international physicians, and this year's meeting boasted record attendance: 27,250 total attendees, 600 more than the previous record set in 1999. Subspecialty Day programs were attended by 7,125 physicians, up 27% vs. last year.

Refractive surgery backdrop: flat to declining procedure volumes for 2006. Our conversations with refractive surgeons painted a clear picture of a LASIK market that has not grown in 2006. Most surgeons report LASIK volumes for this year that are in-line with or slightly lower than last year. In some markets, it is clear that the value-priced providers, such as LCA-Vision's LasikPlus centers, are taking share from surgeon-owned and premium-priced LASIK practices. Consistent with these market trends, TLC Vision announced just prior to AAO that it is aggressively expanding its consumer-focused, value-priced refractive strategy.

Our AAO refractive surgery recap, which begins below, includes reports on the emerging presby-IOL market, the new crystalens Five-O accommodating IOL, sub-Bowman's LASIK surgery, the new VisuMax femtosecond laser from Zeiss, and the AcuFocus intracorneal inlay.

The mood in the Retina community remains upbeat, driven by the rapid uptake of Lucentis and Avastin, for AMD and other indications. Our retina coverage begins on Page 5, with an emphasis on usage patterns and cost/benefit issues associated with AMD treatments. We also highlight new developments in the treatment of diabetic retinopathy : intravitreal Avastin and Lucentis, Eli Lilly's oral medication Arxxant, and the OptiMedica Pascal laser photocoagulator.

A number of new device-based solutions are under development for IOP reduction in glaucoma patients, which have the potential to reduce the reliance on pharmaceutical therapy. Beginning on Page 9, we highlight the new canaloplasty procedure from iScience Interventional, and provide an update regarding selective laser trabeculoplasty (SLT). **Q**

Presby-IOLs: Slow Growth Continues

The presbyopia-correcting IOL market continues to develop at a slower pace than most in the industry had anticipated. We still believe that adoption will eventually increase and that market growth will resume, based on a belief that patients are generally happy with their outcomes, and an expectation that outcomes will only get better as surgeons gain more experience with these lenses and as technology improves.

Some of the key barriers to market growth up to this point:

- **The presby-IOL category has been more challenging than expected for surgeons,** involving significant "chair time" and the need to explain alternative technologies in great detail to patients.

Continued on next page

Presby-IOLs from Page 1

- **Cataract surgeons without a lot of refractive experience are adjusting to more demanding patient expectations.** Some are probably uncomfortable asking for significant out-of-pocket payments, which they have not had to do with Medicare cataract patients. The high out-of-pocket cost to patients is itself a barrier to adoption.

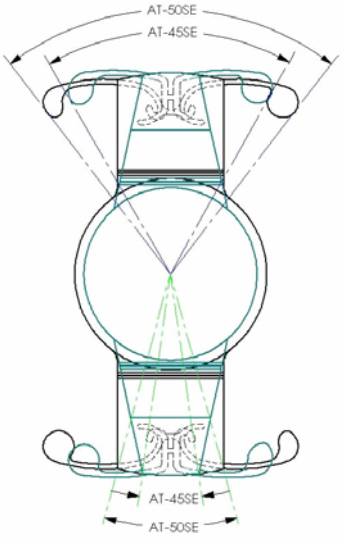
- Each of the three approved IOLs: Alcon's ReSTOR, AMO's ReZoom, and eyeonics' crystalens, has drawbacks and limitations. More than the other two products, Alcon's ReSTOR diffractive multifocal IOL was positioned upon launch as the single best solution for all patients, and the product has not lived up to its initial billing for many surgeons and patients.

The "mix and match" debate that has been so prominent at cataract and refractive conferences over the past year seems to have subsided. Based on feedback from both surgeons and manufacturers, the actual percentage of patients that has been implanted with two different presby-IOLs is rather small. We suspect that the mix/match debate itself, which ultimately highlights the shortcomings of each of the three approved products, has likely contributed to confusion among some surgeons and kept them on the sidelines. At this year's AAO, each of the three manufacturers of approved presby-IOLs seems to have reverted to a more basic marketing approach of promoting its own products and trying to stimulate growth of the overall category. **Q**

Aloha! eyeonics introduces the crystalens Five-O

At AAO, eyeonics introduced crystalens Five-O, the most prominent feature of which is a 5.0mm diameter optic. This is the first new iteration of the company's flagship crystalens accommodating IOL since the launch of the square-edge (SE) version of the 4.5mm diameter lens. The new lens will be priced at $895, consistent with the previous model.

With the introduction of the Five-O, eyeonics now conforms to a "standard" IOL diameter, and addresses one of the key objections that it has faced in the field. The original 4.5mm optic has not been associated with significant glare and halo problems in the real world: the incidence of glare and halos is comparable to standard monofocal IOLs and better than multifocal IOLs. However, competitors have been able to raise concerns regarding the small diameter optic, and many surgeons will be more comfortable implanting a 5.0mm lens.



Source: eyeonics, Inc.

Other new features of the crystalens Five-O include a rectangular plate haptic (with parallel sides) instead of the trapezoidal plate haptic (tapered sides), which should slide more easily in the capsular bag, even after fibrosis. The rectangular plate haptics also provide 17% greater surface area contact with the capsular bag, which should improve predictability, and 88% more plate arc length, which should provide more capsular bag support. Surgeons that have implanted the new crystalens Five-O say that it handles more like a traditional IOL, centers well during implantation, and stays in place better than the previous version during final removal of the viscoelastic. These surgeons also say that the Five-O seems to provide more accommodation than the previous version, although there is not yet any clinical data available to support this observation.

AT AAO, James Davies, MD reported on early results of 18 eyes with the new crystalens Five-O. At the one month time point, 94% of eyes were 20/30 or better uncorrected at distance and intermediate, and 100% were J3 or better uncorrected at near (16 inches). Distance-corrected near visual acuity (DCNVA), which is a measure of accommodative ability of the lens, looks promising in the early going, with 94% of eyes achieving J3 or better at one month post-op. Among a randomly selected group of patients from the FDA study of the original AT45 lens, only 62% had DCNVA of J3 or better at one month.

Jay Pepose, MD, PhD presented results of an 8-site, 5-arm study comparing bilateral crystalens to bilateral ReSTOR, bilateral ReZoom, and mix/match combinations of crystalens and multifocals. Based upon monocular testing, crystalens eyes had statistically better uncorrected and distance-corrected intermediate vision. Crystalens also stood out with respect to contrast sensitivity and subjective vision, and outperformed ReSTOR (but not ReZoom) in the area of uncorrected and best-corrected distance vision. Not surprisingly, ReSTOR performed well with respect to both uncorrected and distance-corrected near vision. In order to improve binocular near vision in patients that initially receive a crystalens in their dominant eye, surgeons including Dr. Pepose and Michael Colvard, MD recommend either (1) a "mini-monovision" approach in the non-dominant eye using crystalens targeted at -0.5 to -0.75D, or (2) a ReSTOR lens in the non-dominant eye. **Q**

SBK: Combining the Benefits of LASIK and Surface Ablation

A number of speakers made a strong case in support of surface ablation over LASIK for laser vision correction, during the opening session of the Refractive Surgery Subspecialty Day program. Surface techniques include PRK, LASEK, and Epi-LASIK. The arguments for and against surface ablation are relatively easy to characterize:

- On the positive side, surface ablation avoids the possibility of flap related complications and the potential for compromised corneal biomechanical strength/ stability.
- On the negative side, surface ablation involves longer visual recovery (sacrificing the LASIK "wow factor") and more postoperative pain.

Marguerite McDonald, MD kicked off the Subspecialty Day program with a talk entitled, "Why I Hung up My Microkeratome." She pointed out that evolving surgical techniques and post-operative drug regimens are addressing the issues of pain and visual recovery. She also referenced two recent unpublished studies, one by David J. Tanzer, MD and another by Anelise Wallau, MD, that report superior wavefront-guided results for surface ablation versus LASIK.

- In the Tanzer study, surface ablation outperformed LASIK with respect to the percentage of patients within +/-0.25D of intended correction (71% versus 56%) and the percentage of patients achieving 20/12.5 or better acuity (70% versus 34%).
- In the Wallau study, PRK resulted in better "achieved versus intended" visual outcomes, significantly less induction of higher order aberrations, and higher patient satisfaction.

The convergence of the increasing focus on corneal biomechanical stability and newly available LASIK-flap-making technology has opened the door to a new hybrid approach. Daniel S. Durrie, MD, drawing on the work of Prof. John Marshall, made a case for a new approach called Sub Bowman's Keratomelusis, or "SBK." (We hope that the refractive surgery industry and/or ophthalmic community will come up with a more marketable name for this procedure.) By making a thin, 100 micron "sub-Bowman's" LASIK flap using a precision femtosecond laser, the fast visual recovery and relative pain-free post-op course of LASIK may be maintained while preserving the corneal stability currently achieved with surface techniques.

Dr. Durrie presented early results of a prospective, randomized contralateral eye study, conducted along with Stephen Slade, MD, comparing SBK and PRK in 100 eyes of 50 patients. SBK was performed using the IntraLase 60kHz femtosecond laser targeting 100 micron flaps. SBK clearly outperformed PRK in uncorrected visual acuity and subjective "better vision" at one day, three days, one week, and one month post-op. By the three month follow-up visit, PRK had caught up to SBK with respect to visual acuity outcomes, and the difference in subjective vision was no longer statistically significant. With respect to post-op pain, SBK out-performed PRK at all time points through one month, with the most significant differences noted during the first week following surgery. **Q**

Carl Zeiss Meditec Unveils the VisuMax Femtosecond Laser

Perhaps the highest profile product introduction at AAO 2006 was the VisuMax Femtosecond Laser System from Carl Zeiss Meditec. It was actually more of an unveiling than a launch: Zeiss hopes to have a CE Mark and FDA 510(k) clearance by the time of the ASCRS meeting in late April, and plans to start selling in the US and Europe by next summer.

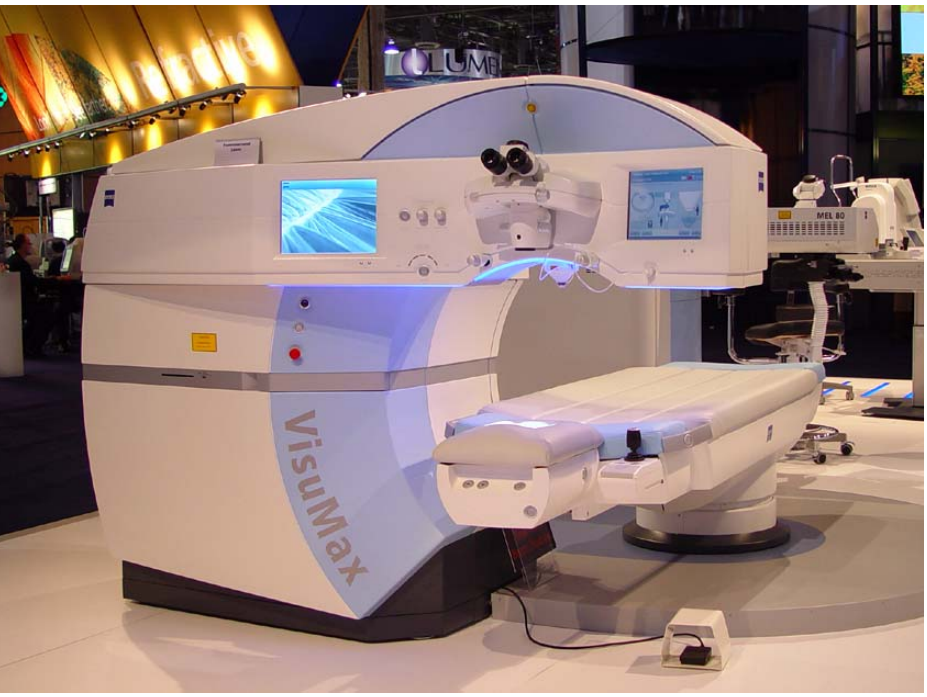
Zeiss is emphasizing improved work flow efficiency arising from the use of VisuMax alongside the company's MEL-80 excimer laser. The two laser systems have a common data interface, and a swiveling bed can quickly move the patient from the FS laser to the excimer. This marketing approach will likely have more appeal in Europe than the US, due to the fact that the MEL-80 only recently received FDA approval and does not have a meaningful installed base in the US. According to Zeiss, some additional product features and benefits include:

- Short laser startup time and no permanent "stand-by" mode
- Highest quality surgical view based on Zeiss optics
- Extremely high depth accuracy and low energy density to minimize side effects
- High pulse rate and short procedure time (we heard mention of a 20 second flap cutting time, but Zeiss is not yet disclosing detailed specifications)
- A spherical/curved contact glass interface with the cornea that provides minimal applanation and IOP increase; a low level of suction is applied only during laser treatment, and no patient so far has lost vision during treatment.

Continued on next page

Zeiss VisuMax from Page 3

In an interesting demonstration of the high precision of the VisuMax system, Zeiss is attempting to perform refractive correction surgery with the femtosecond laser alone. Dubbed "FLEX" (Femtosecond Lenticule EXtraction), the approach involves removal of a disc of corneal tissue to reshape the cornea as an alternative to excimer laser sculpting. The FS laser is used to create the front and back surfaces of this lenticule, as well as a flap to enable removal of the lenticule. At AAO, Zeiss reported results for the first 10 myopic eyes treated with FLEX. Visual acuity and corneal topography outcomes have been better than expected, surprising even company insiders. While this is certainly a fascinating approach and a good demonstration of the capabilities of the VisuMax system, FLEX is still in very early development. Such an approach would require a full PMA process prior to US marketing, and would still have to compete with the versatility and sub-micron precision of the latest excimer laser technology.



With permission from Carl Zeiss Meditec

Product launch is still months away, but the legal battle has already begun. The day before AAO got underway, IntraLase announced that it had filed a lawsuit against Zeiss, alleging that Zeiss "breached an intellectual property agreement with IntraLase by improperly using confidential and proprietary information of IntraLase which Zeiss wrongfully induced IntraLase to disclose. Among other things, the suit seeks damages for breach of contract and payment to IntraLase of all revenues and profits derived by Zeiss from the sale and use of its laser." Zeiss quickly responded with a statement of its own, saying that the IntraLase claims are "completely baseless" and that Zeiss "has not breached any agreement or other obligation to Intralase, nor has CZM otherwise acted improperly."

At this point, it's impossible to handicap the outcome of this legal dispute. Unlike a patent infringement suit, where predicting the outcome is very difficult but an outside observer can at least examine the potentially infringing product vis-à-vis the patent claims owned by another party, this matter involves agreements and conversations to which outsiders are not privy. Handicapping the outcome is also made more difficult due to the fact that both of the companies involved have solid reputations for integrity and innovation. Looking ahead to potential future legal disputes related to the Zeiss VisuMax system, we are not aware of any patent infringement suits that have been filed so far. However, we note that IntraLase has a strong intellectual property position in the field of femtosecond laser technology, and 20/10 Perfect Vision has at least some intellectual property covering laser optics that conform to the anterior surface of the cornea.

Additional femtosecond laser competitive updates:

- **Ziemer Ophthalmic Systems** reported that close to 150 eyes have now been treated using its DA VINCI Femtosecond Surgical Laser system in a commercial setting, with good results. The manufacturing supply chain is in place, and 50 units are currently being produced. The company continues to talk to potential US sales and marketing partners, but for the next 2-3 months the company's top priority will continue to be the commercial rollout in Europe.
- **20/10 Perfect Vision** has developed a faster version of its FEMTEC system that will be more competitive than the original system within the LASIK market. This upgraded system is fully launched in Europe, but is still awaiting FDA 510(k) clearance in the US. Because of this, the company has not provided an update regarding its US launch plans.
- **WaveLight AG** is still developing a femtosecond laser system, but has not provided an update regarding its progress since last year's AAO. **Q**

AcuFocus Intracorneal Inlay: Improved Near Vision for Presbyopes Through Increased Depth of Focus

Intracorneal inlays continue to show promise as a future option for surgical presbyopia correction. While accommodating and multifocal IOLs should continue to be the solutions of choice for older presbyopes, particularly those with any stage of cataracts, younger (pre-cataract) presbyopes will likely opt for cornea-based solutions. These include CK (conductive keratoplasty), multifocal/presby-LASIK, and intracorneal inlays. In our recent ESCRS review (EyeQ Report No. 7), we highlighted promising early results with the ReVision Optics PresbyLens intracorneal inlay for presbyopia.

At AAO, George Waring, MD presented encouraging early clinical data for the AcuFocus ACI 7000 intracorneal inlay. Sometimes referred to as a "pinhole" inlay, the product consists of a thin opaque ring that is implanted under a corneal flap, centered over the visual axis. The outside diameter of the ring is 3.8mm and the inside diameter measures 1.6mm. It is implanted in the non-dominant eye of emmetropic presbyopes, and is designed to increase depth of focus by creating a small "f22" aperture, thereby improving near vision while having a minimal impact on distance vision. AcuFocus claims that the inlay provides near correction equivalent to about 2.5D. Like other corneal inlays, the ACI 7000 is easily removable if the patient is dissatisfied with the outcome or if the patient's vision correction requirements change.

Visual acuity results for the AcuFocus inlay, from a study conducted in Istanbul, were presented at AAO. Of 39 eyes implanted, 34 have been followed to 12 months. The inlay did not affect the cohort's mean uncorrected distance visual acuity, which remained 20/20 at all time points, although two patients had the inlay explanted due to dissatisfaction with loss of distance vision. Mean uncorrected near visual acuity improved significantly, from J6 (20/50) pre-op to J1 (20/20) at months 1 and 3 and to J1+ (20/16) at months 6, 9, and 12. At 12 months, 33 of 34 patients (97%) were spectacle-free.

The FDA IDE clinical trial for the AcuFocus inlay will expand in 2007. The initial phase of the three-year, Phase II study began in February 2006, enrolling 75 patients at seven sites. Beginning early next year, the expansion phase of the study will enroll 400 patients at up to 20 sites. **Q**

Avastin and Lucentis: New Treatments of Choice for Wet AMD

Since the FDA approval on June 30, 135,000 doses of Lucentis (ranibizumab) have been administered to over 48,000 AMD patients, according to George Williams, MD speaking at an AAO press conference.

At the Retina Subspecialty Day, Philip J. Rosenfeld, MD, PhD provided an update on the off-label use of intravitreal Avastin (bevacizumab). Intravitreal Avastin for wet AMD is currently being reimbursed in 48 out of 50 states; the Medicare carrier for Nebraska and Kansas is the only one that is not currently providing coverage for this treatment. In the year-and-a-half since intravitreal Avastin was first used to treat AMD, numerous investigator-led studies have been initiated. So far in 2006, there are over 60 PubMed references to intravitreal Avastin. At AAO, there were 22 posters, 4 papers, and an instructional course covering this topic. So far, intravitreal Avastin has been shown to be safe, with no indication from available studies or surveys of toxicity, significant inflammation, or signals of systemic adverse events. In terms of efficacy, Avastin is decreasing retinal thickness on OCT and providing modest improvements in visual acuity for a number of proliferative/exudative retinal conditions.

A snapshot of Avastin and Lucentis usage during September 2006, based on survey responses of 227 US-based ASRS members, was presented by Dr. Rosenfeld. The "PAT Mini-Survey" was conducted by Robert Mittra, MD and John Pollack, MD. Retina specialists were presented a list of AMD treatments asked which one they usually recommend to patients with neovascular AMD:

- **For patients that have Medicare but no secondary insurance,** 70% of physicians usually recommend Avastin, 20% recommend Lucentis, and 7% recommend one of these drugs in combination with PDT. Only 3% usually recommend other treatments, including Macugen and PDT, alone and in combination.

- **For patients that have Medicare with secondary insurance,** 49% of physicians usually recommend Avastin, 39% recommend Lucentis, and 7% recommend one of these drugs in combination with PDT. Only 5% usually recommend other treatments, including Macugen and PDT, alone and in combination.

Continued on next page

Lucentis and Avastin from Page 5

There are two key takeaways from these survey results. First, Genentech's two anti-VEGF products have almost completely supplanted both Visudyne/PDT and Macugen as the preferred treatments for wet AMD. Second, even for fully insured patients, as of September, Lucentis had not replaced Avastin as the preferred treatment. Dr. Rosenfeld said that these survey results surprised him, because it had been assumed by many that once Lucentis received FDA approval and Medicare reimbursement was established, usage would shift quickly from Avastin to Lucentis, particularly for patients with secondary insurance. He noted that these survey results were from September, and that Lucentis usage has likely increased since then. (Indeed, some retina specialists with whom we spoke at AAO pegged the current relative usage of Lucentis at 60-80%.) Dr. Rosenfeld's conclusion: "Money matters," and because there is a perceived equivalence between these two drugs, cost weighs heavily as a factor.

The experience to date from 1,374 treatments with intravitreal Avastin at the New York Eye and Ear Infirmary was reported in a scientific poster. Patients have been treated for choroidal neovascularization, neovascular glaucoma, and macular edema. So far, among AMD patients treated, 38% have gained three or more lines of visual acuity, another 34% have at least maintained vision, and 28% have lost 1-2 lines of VA. Among macular edema patients, 87% have improved VA by at least one line. Among neovascular glaucoma patients, regression of rubeosis was noted within one week. There have been no reported cases of endophthalmitis or retina detachment, and there have been three cases of mild inflammation that resolved.

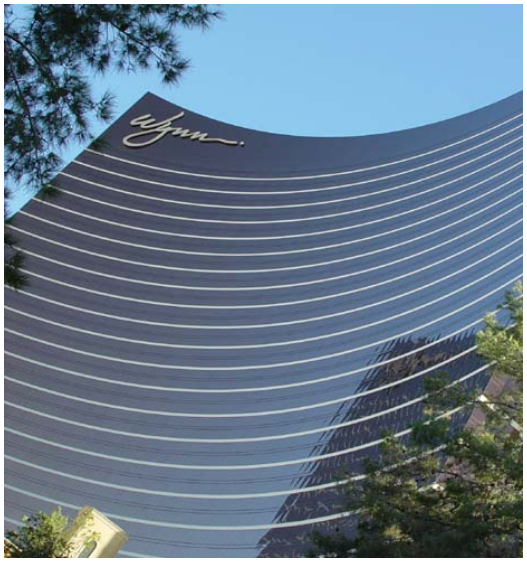
NEI/NIH to Sponsor Head-to-Head Study of Lucentis and Avastin

In early October, the National Eye Institute (NEI) of the National Institutes of Health (NIH) announced that it will fund a new multicenter clinical trial to compare Lucentis and Avastin for the treatment of advanced AMD. During the Subspecialty Day program, study chairman Daniel Martin, MD provided an overview of the study, entitled CATT (Complications of Age-Related Macular Degeneration Treatment Trials). The study will enroll about 1,200 patients with newly diagnosed AMD, randomly assigned to one of four groups: (1) Lucentis with four week dosing; (2) Avastin with four week dosing; (3) Lucentis with variable dosing; and (4) Avastin with variable dosing. The primary outcome measure will be mean change in visual acuity.

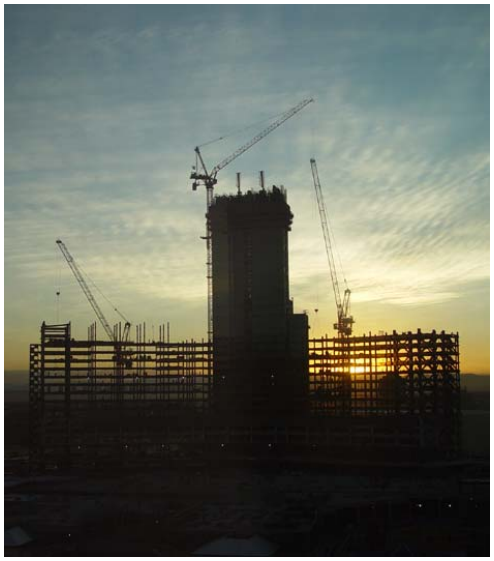
The study will follow patients for two years and will take about four years to complete. Enrollment is scheduled to begin in early 2007, and one year follow-up data will be reported in 2009. The study will be conducted in 40 centers in the US; 20 have already been selected, and 20 additional centers will be selected by early 2007. NEI/NIH is emphasizing that this is more than just a cost study, and that the primary goals are to better understand the safety and efficacy of intravitreal Avastin and to develop better dosing/re-treatment guidelines for both drugs. **Q**

Past, Present, and Possible Future of AMD Therapy...

Visudyne and Macugen



Lucentis



Avastin

Economic Analyses: Cost Effectiveness of AMD Therapies

Some interesting data points regarding the growth in utilization of retinal services and the highly variable cost of AMD treatment were highlighted by William L. Rich III, MD, the AAO's Medical Director for Health Policy, at an evening symposium on AMD treatment strategies:

- Between 2001 and 2004, the number of intravitreal injections in the US grew from about 4,500 to about 83,000.
- Between 1999 and 2004, the number of OCT diagnostic exams increased twenty-fold, from 153,000 to 3.11 million.
- Total two-year costs of AMD treatments, including products and services: Avastin $2,037, Visudyne $11,162, Macugen $27, 276, and Lucentis $67, 128.

A rigorous analysis to determine the relative cost of a line of vision in AMD was reported in a scientific poster by William Smiddy, MD of Bascom Palmer. Outcomes data was compiled from a number of published studies, including TAP, AREDS, and ETDRS. Costs were inclusive of office visits, diagnostic testing, and treatments. Results were reported in terms of cost per line-year of vision saved. Among AMD treatments that have been available for some time, approximate costs per line-year saved were as follows: Juxtafoveal or subfoveal laser: $176; PDT for classic lesions: $448; PDT for occult lesions: $551; PDT plus IVTA; $66; Macugen: $1,248; and vitamins $473. Newer treatments (Lucentis and Avastin) were given a more cursory analysis, due to the relative lack of data available. Initial estimates of cost per line-year of vision saved for Lucentis and Avastin were $900 and $60, respectively. Based on this analysis, Avastin is the most cost-effective AMD treatment currently available (15x more cost effective than Lucentis), and Macugen is the least cost effective.

In order to emphasize the significant difference in cost between Lucentis and Avastin, Retina Subspecialty Day panel moderator H. Richard Johnson, MD posed the rhetorical question, "Given the number of children that could be immunized with the savings from one Avastin treatment, can you justify the use of Lucentis?" **Q**

Diabetic Retinopathy: Highlighting Advances in Pharmaceutical and Laser Treatment

Lucentis and Avastin Show Promise for Diabetic Retinopathy and Diabetic Macular Edema

Because of the success of anti-VEGF agents Lucentis and Avastin in treating neovascular AMD, they are also being studied in diabetic retinal diseases. Results so far are very encouraging. The following paragraphs highlight presentations of interest from the Retina Subspecialty Day program and the scientific poster session.

Peter Campochiaro, MD reported on a prospective, open label Phase I pilot trial of Lucentis in 20 eyes of 20 patients with severe DME at The Johns Hopkins University. The vast majority of eyes in the study (18/20) had already been treated with focal laser and/or intraocular steroids. Patients received five intravitreal injections of Lucentis: an initial injection plus repeat doses at months 1, 2, 4, and 6. Lucentis treatments were well tolerated, and produced marked improvement in DME symptoms. Median excess foveal thickness was reduced by 300µm (97% reduction) at month 7 and by 240µm (77% reduction) at month 12, which was a full six months after the last Lucentis injection. Median visual acuity was improved by 10 letters at month 7 and by 7 letters at month 12.

Robert L. Avery, MD discussed his experience with Avastin for proliferative diabetic retinopathy (PDR). Avastin has a rapid anatomic effect in eyes with PDR, although neovascularization recurs after a variable period of time and re-treatment is needed within months after the initial dosing. Dr. Avery also stressed the value of intravitreal Avastin as an adjunct to vitrectomy surgery for treatment of severe PDR; administered several days before surgery, it appears to be effective in reducing intraoperative bleeding.

John Mason III, MD reported on results with intravitreal Avastin in 39 eyes of 34 patients with refractory DME. These patients had already undergone previous treatment with focal laser, intravitreal steroids, or vitrectomy with ILM peeling. Short term results were favorable for this challenging group. Mean acuity at baseline and at one and three months was 20/111, 20/87, and 20/89, respectively. Mean central macular thickness at baseline and at one three months was 357µm, 308µm, and 309µm, respectively.

Continued on next page

Diabetic Retinopathy from Page 7

Arxxant for Diabetic Retinopathy: Encouraging Outcomes but Long Road to Approval Remains

Arxxant (ruboxistaurin) from Eli Lilly is an investigational oral medication for the treatment of moderate to severe non-proliferative diabetic retinopathy (DR). The first of a new class of compounds being investigated for the treatment of this condition, it works by limiting the overactivation of protein kinase C beta (PKC beta), a naturally occurring enzyme that has been linked to the development of DR.

Lilly submitted a new drug application (NDA) to the FDA for ruboxistaurin in February 2006, and received an approvable letter from the FDA in August 2006. The FDA has indicated it will require efficacy data from an additional Phase 3 study before it will consider approving the molecule. Lilly has decided to appeal the FDA's decision and has recently begun discussions with the agency. As noted in the accompanying article below by Kelly Close, there is doubt within the diabetes community that ruboxistaurin may ever come to market.

Additional positive results were recently reported from a three-year phase 3 clinical trial (the PKC- DRS2 study) in which ruboxistaurin reduced the risk of sustained moderate vision loss by 40% when compared to placebo in patients with moderate to severe non-proliferative DR. The study involved 685 patients that had moderate to severe nonproliferative diabetic retinopathy at the start of the study.

- Vision loss (measured in the study as sustained moderate vision loss, or SMVL) occurred in only 5.5% of patients treated with ruboxistaurin compared to 9.1% of patients treated with placebo, equaling a 40 percent relative risk reduction (P=0.034) over three years. Vision loss (SMVL) was defined as a three-line loss on a standard eye chart that was sustained for at least 6 months.
- Mean visual acuity was better in the ruboxistaurin-treated patients after 12 months. Baseline-to-endpoint visual improvement of greater than or equal to 15 letters was more frequent (4.9% versus 2.4%) and greater than or equal to 15 letter worsening was less frequent (6.7% versus 9.9%) in ruboxistaurin-treated patients compared with placebo (P=0.005).
- The beneficial effect of ruboxistaurin was not accompanied by a reduction in the progression of study patients from non-proliferative to proliferative DR.

Continued on next page

Viewpoint: New Phase 3 Trial Required for Ruboxistaurin for Diabetic Retinopathy

By Kelly L. Close

In a blow to Lilly (as well as to patients), the FDA in August sent an approvable letter to Lilly for ruboxistaurin, meaning the drug is not approvable at this time but may become approved with more data. The FDA clarified on September 29 that it would require another three-year efficacy trial for further clinical evidence.

The ruboxistaurin submission was originally risky because Lilly only submitted one "real" phase 3 trial; it seems that will not be enough so it's likely we can bid farewell to the chances for this drug to survive. Pity! Critics say that Lilly rushed the trial and didn't plan a proper submission. It is hard to argue with that. The question is whether Lilly will stick with the product – we think it is quite likely that the company will walk away because another multi-year wait would limit patent life, though we estimate the company would have patent protection until 2017.

Basically, anyone smart about Lilly shakes their head in disgust when you even begin to ask the question: *"Ruboxistaurin? Forget it! That's dead!"* We are disappointed that it looks like this drug won't be added to the armamentarium to treat patients. While it may not have seemed a major blockbuster-in-the-making, it did look like it had real potential to help patients prevent or treat microvascular risk – a serious need. Analyst estimates had been about $500 million for this indication, but we had thought that sounded low, long term. We had also thought Lilly would do more trials showing it could prevent/treat other microvascular complications and that it would be used for this off label, anyway. The FDA's action is a dismal signal to other companies about how hard it is to get drugs approved for complications – and also a critical signal about the importance of investing in and getting buy in on very solid trial design very early. **Q**

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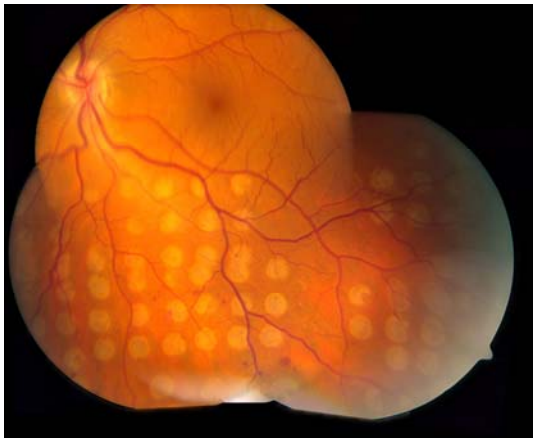
OptiMedica Pascal Photocoagulator Makes Laser Therapy Faster and More Comfortable

At the same time that progress is being made with drug therapy for diabetic retinopathy, laser technology is moving forward as well. Earlier this year, privately held OptiMedica Corp. introduced the Pascal Pattern Scan Laser Photocoagulator. The US launch took place in January and CE Mark approval in Europe was granted in September. The system has FDA 510(k) clearance to treat a variety of retinal diseases, but initial usage is focused on diabetic retinopathy (DR) and diabetic macular edema (DME).

The Pascal Photocoagulator can deliver a single shot or a predetermined pattern array of up to 25 spots delivered in a rapid sequence. The primary benefits over standard lasers are significantly reduced procedure time (up to seven times faster), the potential for fewer treatment sessions, and a substantially more comfortable experience for the patient. The Pascal system was highlighted in Retina Subspecialty Day presentations by Mark Blumenkranz, MD and Harry Flynn, Jr., MD. At the American Society of Retina Specialists (ASRS) annual meeting in Cannes in September, Julia Haller, MD reported that over 1,200 patients had been treated so far at five leading retina centers, with safety and efficacy comparable to single-spot delivery lasers but with superior physician and patient acceptance. **Q**



Source: OptiMedica Corporation

Glaucoma: Device-Based Alternatives to Medical Therapy

iScience Introduces Canaloplasty Procedure for IOP Reduction

Canaloplasty, a new surgical approach to intraocular pressure (IOP) reduction, was launched at AAO. Privately held iScience Surgical has been re-named iScience Interventional, and the company is developing a new generation of "interventional ophthalmology" procedures under the "iCath" brand. The first such microcatheter-based procedure is canaloplasty, which involves cannulation and 360° dilation of Schlemm's canal. Although the company's canaloplasty products are not labeled specifically for glaucoma and IOP reduction, it is clear that this is the ultimate application for this procedure. Over 200 patients have been treated so far worldwide.

The goal of canaloplasty is to re-establish circumferential outflow from Schlemm's canal in patients with glaucoma, and to do so without penetrating deep into the eye or creating a bleb. The procedure involves (1) creation of a scleral flap, (2) dissection to Schlemm's canal and insertion of a flexible "iTrack" microcannula which incorporates a lighted beacon, (3) injection of viscoelastics to dilate the entire canal and collector system, and (4) passage of a 10-0 Prolene suture to establish tension and maintain patency of the canal.

At the Glaucoma Subspecialty Day program, Richard A. Lewis, MD presented results of a 12 month prospective multicenter study in eyes with open angle glaucomas. Mean IOP was reduced from 25.4mm Hg pre-op to under 16mm at 3 and 6 months, and to 14.9mm at 12 months, representing a roughly 40% drop. At 12 months, 76% of eyes were considered an "unqualified success," with IOP<18mmHg and no concurrent medications. An additional 6% of eyes were categorized as a "qualified success," reaching this IOP target with the help of medications.

Advantages of canaloplasty include a low risk of complications and easy post-op care due to the lack of a bleb.

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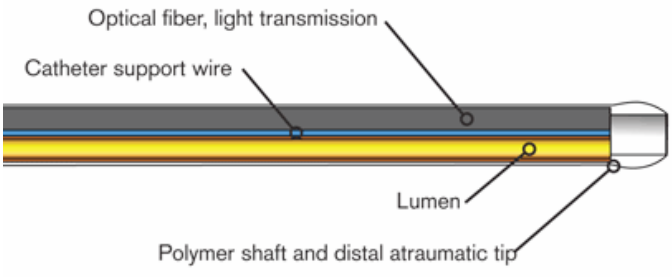
Dr. Lewis pointed out that there is a learning curve involved in identifying the canal and performing the procedure, and that establishing the correct suture tension is critical – insufficient suture tension results in insufficient IOP reduction. In the scientific poster session, Dr. Lewis quantified the effect of suture tension by comparing the IOP results from two groups of eyes: those with little or no tensioning versus those with "slight" trabecular tensioning.



Source: iScience Interventional, Inc.

At 12 months, subjects with low tension had mean IOP of 17.0mmHg and were taking an average of 0.9 medications; subjects with greater tension had mean IOP of 13.7mmHg and were taking an average of 0.2 medications.

Canaloplasty will not be considered as first-line therapy for glaucoma any time soon, given the newness of the approach, the small amount of supporting clinical data so far, and the lack of an explicit labeled glaucoma indication for the iScience products. However, as surgeons become familiar with the technique, they may choose it ahead of other surgical approaches for glaucoma patients that fail on medical therapy.

SLT Steps Up its Challenge to Eye Drops as First-Line Therapy for Glaucoma

Our discussions in recent months with ophthalmologists from a variety of sub-specialties indicate that selective laser trabeculoplasty (SLT) is increasingly becoming a first-line alternative for glaucoma patients. SLT, which utilizes the Selecta II laser manufactured by Lumenis, was introduced in the US about five years ago. The company says that there are over 1,000 of its lasers currently in use for SLT in the US. SLT reduces IOP by improving aqueous outflow without the coagulative damage to the trabecular meshwork caused by argon laser trabeculoplasty (ALT). Because of the high cost, potential side effects, and well-documented compliance issues associated with glaucoma medications, ophthalmologists are increasingly offering SLT to their patients prior to prescribing eye drops.

At the scientific poster session, L. Jay Katz, MD presented results from the first multicenter study comparing SLT with medical monotherapy using prostaglandins. The prospective, randomized, controlled trial covered 136 eyes of 72 patients, treated at 17 sites. At the 8 month follow-up interval, IOP reduction was comparable in the medication and SLT groups. The medical therapy cohort had mean IOP reduction from 25.0 to 17.3mmHg (-31%), and the SLT cohort had mean IOP reduction from 24.7 to 18.0mmHg (-27%). A majority of patients in each arm of the study was within 2mmHg of target IOP. **Q**