Trends-in-Medicine

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by Lynne Peterson

SUMMARY

OSI/Eyetech's Macugen is trying to find a place in the U.S. as maintenance therapy for wet AMD in conjunction with Genentech's Avastin or Lucentis, but many retinal specialists were dubious that the company can hang on long enough and convince enough doctors – and payors – that this is the right approach. ♦ DME trials no longer must be three years; a 2-year trial may be acceptable to the FDA if two statistical hurdles are met. ♦ It appears the FDA may let Allergan change the primary endpoint in the second Phase III memantine glaucoma prevention trial (and without a statistical penalty). ♦ Corneal staining is not raising significant concerns. The increase in *Acanthamoeba* keratitis is being blamed on changes in residential water treatment processes and poor patient contact lens hygiene, not contact lens materials or solutions. Differences in the various contact lens solutions are viewed mostly as marketing ploys. ♦ Regeneron's VEGF-Trap may find a role in AMD despite the success of Avastin and Lucentis. ♦ Two products to watch: SurModics' I-vation implant for DME and Othera Pharmaceuticals' OT-551, a topical therapy for AMD.

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ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY (ARVO)

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This was a busy ARVO. The focus was on anti-angiogenesis, but not just on age-related macular degeneration (AMD), and not just on Genentech's Avastin (bevacizumab) and Lucentis (ranibizumab), but on other anti-VEGFs in development and how to use all of these agents in other ocular conditions. There was also news on many other topics, including keratitis, antibiotics, diabetic macular edema (DME), dry eye, glaucoma, and more.

Acanthamoeba Keratitis and Corneal Staining

Acanthamoeba causes a rare, difficult-to-treat chronic keratitis, *Acanthamoeba* keratitis (AK), and it is getting a lot of attention because of an increasing U.S. incidence. *Acanthamoeba* is a free-living protozoa found in most sources of water and soil. It was first recognized as an eye pathogen in 1973 in southern Texas, but it is uncommon, occurring in about 1 in 500,000 contact lens users per year (which translates to an expected rate of ~60 cases per year), but not all cases are contact lens-related.

On March 7, 2007, the Centers for Disease Control and Prevention (CDC) started an investigation into the increased incidence of *Acanthamoeba* keratitis. They are currently in the case-finding stage.

At the American Society of Cataract and Refractive Surgeons (ASCRS) meeting in April 2007, Dr. Elmer Tu of the University of Illinois at Chicago (UIC) reported that there has been a "dramatically increasing incidence" of *Acanthamoeba* keratitis. Dr. Tu suggested the problem is city water treatment methods, explaining that the Environmental Protection Agency (EPA) in 1998 mandated that water treatment facilities reduce the amount of carcinogenic byproducts. The new rule was implemented in 2002 for large water systems and in 2004 for smaller systems. Dr. Tu said the *Acanthamoeba* problem is multifactorial, but the water treatment changes account for the vast majority of the increase in *Acanthamoeba* infections, "Our hypothesis is that this has resulted in microbial over-growth, which is the food for *Acanthamoeba*."

Dr. Tu and other researchers from UIC – particularly Megan Shoff M.D. and Charlotte Joslin O.D. – and Ohio State University (OSU) reported at ARVO that the AK cases in Chicago do not result from a new, novel AK genotype. Rather, the Chicago AK isolates are very closely related to known AK isolates, which means that there is no support for the hypothesis that the Chicago isolates are a more pathogenic, unknown genotype, and it means that there is support for their

hypothesis that the increase in AK in Chicago may be due to the changes in chemical treatment of the household water supply.

They also reported on the prevalence of *Acanthamoeba* in tap water taken from toilet tanks in 134 homes in the Chicago area between June and December 2006. They found:

- Amoeba in 55.2% of homes sampled, and they suggested this may underestimate the true level of amoebic colonization.
- *Acanthamoeba* in 17.9% of homes.
- *Acanthamoeba* and/or another amoeba in 58 of the 111 zip codes tested.

While changes in water treatment may explain the increased risk of AK, these researchers also pointed to two other factors that need to be considered:

1. **Accuracy of lab analyses.** A poster reported on significant differences in the ability of laboratories to accurately culture and identify *Acanthamoeba* keratitis. The researchers had superficial scrapings from patients cultured and genetically typed by two laboratories – the UIC Clinical Laboratory and OSU's lab. The culture rate at the UIC lab was 39.1%, but at OSU it was significantly higher – 92.3% ($p<.001$). Furthermore, in 19 samples analyzed by both laboratories, the OSU lab far outperformed the UIC lab (94.7% vs. 42.1%, $p=0.0044$).
2. **Showering with contact lenses.** A different study which found an association between frequent showering while wearing contact lenses and an increased risk of AK.

In another study, U.K. researchers found over-wear of contact lenses was associated with an increased risk of keratitis, but a researcher said they couldn't say whether this was related to the contact lens solution used or the contact lens material. He said, "Iron deposits are associated with corneal staining, but they are not associated with an increased keratitis risk. Iron is not a pre-disposing factor, but if the cornea is breached, the keratitis risk increases."

Other comments on corneal staining and AK included:

- *Iowa:* "About 80% of *Acanthamoeba* keratitis is related to contact lenses, but ***not*** to specific solutions or contact lens materials."
- *Illinois:* "I could see the FDA requiring a change in the criteria for approval of new contact lens solutions."
- *Massachusetts:* "The AK increase could be contact lens material-related, but it is more hygiene-related."
- *Maryland:* "We are doing a multicenter study, looking at contact lens solutions, contact lens cases, and contact lens materials, but the number of AK cases is small. I suspect corneal staining does make a difference."
- *Florida #1:* "I'm not concerned with corneal staining."
- *Florida #2:* "Our AK cases are not in any patients using silicone hydrogel lenses. All of the solutions are the same – none of them kill *Acanthamoeba*. Corneal staining does increase the risk of keratitis, but I'm not sure this is black and white. Corneal staining doesn't alarm you in contact lens patients; a lot of contact lens patients have it. Bad lens hygiene is more an issue."

ANTI-ANGIOGENESIS

VEGF inhibitors – OSI Pharmaceuticals/Eyetech's Macugen (pegaptinib) and Genentech's Avastin and Lucentis – are being used and tested in a variety of ocular disorders beyond wet age-related macular degeneration (AMD). Among the numerous studies discussed or presented at ARVO were:

- **Diabetic macular edema (DME).** (*See VEGF Inhibitors for DME on page 10.*)
- **CNV secondary to causes other than AMD.** A single-center, open-label, Phase I study of Lucentis in this disorder has 7 patients enrolled, but, after discussion with the FDA, the protocol was changed to use only the 0.5 mg dose. A speaker said, "The majority of patients have a gain in vision, but there are several patients who begin to experience vision loss in the 3-5 month range. There is an early, rapid reduction in central retinal thickness, and then it is fairly stable."
- **Retinal vein occlusion (RVO).**
  - **Lucentis** is being studied in a Phase II trial comparing sham to 0.3 mg and 0.5 mg doses. California researchers also reported that they have found you have to dose Lucentis "pretty frequently" so a drug delivery route might be better for most patients – unless a way to administer Lucentis or Aventis long-term was developed.
  - A poster indicated that **Macugen** seems to work – and might have a role – in the treatment of RVO.
  - A Michigan researcher reported that, based on a retrospective look at 36 patients, **Avastin** is also useful in RVO. Another poster reported that Avastin works for RVO and is safe but has a limited duration of effect (~8 weeks). A third poster by researchers at Bascom Palmer Eye Institute found 80% of RVO patients need a second injection.
  - A speaker commented that the dose of a VEGF antagonist "probably has to be ***increased*** (in RVO patients) with more ischemia."
- **Retinopathy of prematurity (ROP).** A poster also suggested that Avastin may have utility in ROP, and a researcher from Mexico said he is already using it for that off-label, "In the past year I haven't used one single laser for ROP in our hospital. This is the model illness for a VEGF inhibitor."

There were also some warnings about safety issues with anti-VEGF agents:

- Taiwanese researchers reported on two cases of retinal hemorrhage with intravitreal **Avastin** for AMD. They recommended avoiding anterior chamber paracentesis if Avastin is used. But they did not recommend against Avastin use.
- A poster by Florida researchers warned that **Avastin**, **Lucentis**, and **Macugen** all result in "very significant, transient increases in IOP that may be damaging to the optic nerve, particularly in patients with advanced glaucoma." They noted that Lucentis and Avastin appear safe due to the smaller injection volume, but they contended that Avastin is worse than Lucentis at 21-30 minutes, but not sufficiently worse to say Lucentis should be used instead of Avastin.
- Researchers from several countries reported that tractional retinal detachment has occurred in late-stage severe proliferative diabetic retinopathy patients with **Avastin**. They speculated that this is a class effect, but the numbers are small for firm conclusions.
- The National Cancer Institute's **fenretinide**, a known anti-cancer agent, was shown by UCLA researchers to be ***pro-***angiogenic, not anti-angiogenic, in a mouse model. In that study, lesion size and lesion volume increased with fenretinide, and researchers warned, "For wet AMD, this drug has to be viewed with caution."

Researchers from Germany reported on their rat cell culture study comparing Avastin, Lucentis, and Macugen. They found all three significantly suppress choroidal endothelial cell proliferation, but at currently used doses, none was superior over the others in endothelial cell growth inhibition, which one of the researchers called surprising. However, he added, that he thinks there are big clinical differences, with Lucentis and Avastin better than Macugen.

In the U.K., NICE is due to make a decision on Macugen and Lucentis (not Avastin) in September 2007. In the meantime, a U.K. doctor estimated that about a third of NHS Trusts are approving Macugen and Lucentis. A four-arm head-to-head trial is underway in Liverpool comparing photodynamic therapy (PDT), Macugen, Lucentis, and Avastin. He said to watch for data at ARVO 2008 or the American Academy of Ophthalmology 2008.

Dr. Peter Campochiaro of Johns Hopkins discussed his mouse studies of the safety of chronic blockade of VEGF in the eye. He said that, in mice, blockade over a long time (7 months) showed no identifiable functional loss by ERG-B wave amplitude and no increase in apoptosis, with a normal retinal structure. He concluded, "At least at an ultrastructural level, we can't identify any structural damage to the retina." However, he said there was a recent paper in the ***American Journal of Pathology*** which suggested there may be ganglion cell loss with long-term VEGF suppression.

GENENTECH'S Avastin

A poster by an Israeli researcher reported that the half-life of Avastin is 10.2 days in rabbits (~5-6 days in humans), while Lucentis's half-life in monkeys and humans is 3.2 days. He said, "We inject Avastin and Lucentis on the same schedule once a month, but maybe it should be less often, and this may explain why Avastin lasts longer than Lucentis. ***If*** Avastin is equivalent to Lucentis, then maybe we can inject Avastin every 6-8 weeks.

A poster by California researchers found that intravenous (systemic) micro-doses of Avastin (1.25-2.5 mg) can have an ocular effect. He suggested that the IV Avastin dose could potentially be increased to 10-20 mg, which is still far below the systemic dose used in cancer of 400 mg, and have even more ocular effect.

Avastin has previously been shown to have a small effect in AMD on the fellow eye even when that eye is not injected. An expert at ARVO said that new data indicate that Avastin's effect on the fellow eye may ***not*** be from transport through the blood, but how it gets to the fellow eye is not yet known.

OSI PHARMACEUTICALS/EYETECH'S Macugen

Most retinal specialists questioned at ARVO thought Macugen is dead or dying. They no longer see any role for it. Pfizer has given up its U.S. rights to Macugen but remains a partner outside the U.S. However, sources do not believe there is any chance of Pfizer getting involved with Macugen again in the U.S. An OSI official said Pfizer will not get re-involved with Macugen, and OSI is shopping Eyetech – in whole or in part – but hasn't yet found a buyer, so the outlook for Macugen will depend on what a new buyer wants to do.

Comments on the outlook for Macugen included:

- *Pennsylvania:* "There is no role for Macugen going forward – not even a niche. It will fade away. The others (Lucentis and Avastin) just perform much, much better."
- *Mexico:* "There is no role for Macugen. Avastin and Lucentis are equivalent, and we use Avastin because of cost."
- *Germany:* "We stopped using Macugen completely. We were rather disappointed in the results. But perhaps we will use Macugen for Lucentis or Avastin failures out of desperation."

Dr. Michael Tolentino of the Center for Retina and Macular Disease in Winterhaven FL made a fairly strong case for the use of Macugen as maintenance therapy in conjunction with either Lucentis or Avastin. He said, "We wanted to answer a basic science question, but it is coined as a clinical question: Will bevacizumab (a pan VEGF isoform inhibitor) induction, followed by Macugen (a selective $VEGF_{165}$ inhibitor) with either Lucentis or Avastin boosters be efficacious in rescuing patients who have previously been on Macugen or PDT monotherapy?...This is a real world problem."

In Dr. Tolentino's IRB-approved, retrospective, interventional study, 53 patients with 56 treated eyes (44% occult, 25% predominantly classic) have been followed for six months (and 45 of these have 1-year follow-up). All patients started with either Macugen or PDT, then got one intravitreal injection of Avastin (1.25 mg), followed by Macugen every six weeks. After three months, patients could be continued on Macugen alone or could receive – at any time, as warranted – either an Avastin or a Lucentis booster. He found:

- 34% gained ≥3 lines of vision in the first three months (Avastin + Macugen).
- 36% gained ≥3 lines of vision at 6 months (Macugen plus 1-2 injections of Avastin).
- 33% gained ≥3 lines of vision at 12 months.
- At 6 months, patients had gotten an average of 3.2 Macugen injections and 1.4 Avastin or Lucentis injections – (1 injection every 5 weeks). He could not say yet how many boosters patients received in these six months.
- At 12 months, patients had gotten an average of 5.5 Macugen injections and 2.0 Avastin or Lucentis injections – (1 injection every 7 weeks).
- Adverse events included: 1 anaphylactic reaction after an Avastin injection, 1 stroke 4 days after Avastin with full recovery (a typical pan VEGF-type of stroke), 3 patients who required an adjustment in their hypertension medications, and 2 cases of iritis.
- Macugen appears to be able to maintain visual gains observed in patients who have gained vision from a non-selective VEGF inhibitor (Avastin or Lucentis).

Dr. Tolentino said, "My hypothesis is this (approach) works… Once you get rid of the pan isoform and then maintain or stop reinitiation (of neovascularization) with a selective inhibitor, you can still maintain vision to the desired amount…This strategy may be valuable in minimizing systemic exposure to pan isoform inhibitors in the long term and provides an alternative treatment regimen for our AMD patients."

The group of patients who may benefit most from Macugen is diabetics. Dr. Tolentino said, "Where this drug (Macugen) will make its mark is in diabetics because of safety issues…In non-diabetics, the risk of a myocardial infarction (MI) is 3%. In patients with a prior MI, the risk is ~20% for another MI. The risk of an MI in a diabetic is 20%."

Safety is a key reason Dr. Tolentino believes Macugen will continue to have a role. Macugen, he pointed out, has no CV safety signal in its Phase III trials, while Avastin has a black box warning, and Lucentis showed a statistically significant increase in stroke in an interim data analysis of the SAILOR trial – 1.2% with Lucentis 0.5 mg vs. 0.3% with placebo (p=0.02). He said, "If we can improve safety, that is the way we should go…I thought we would help prevent cardiovascular events (with Lucentis and Avastin), and this is not quite true." Dr. Tolentino says he has switched from Avastin to Lucentis because "he had some bad experiences" with Avastin – two cases of patients at 4 mg who got 2 injections and developed capillary hypoperfusion (non-perfusion), which he had seen years ago in monkeys."

The 1,000-patient LEVEL trial – funded by Pfizer/Eyetech – was designed to answer the question of whether Macugen is good maintenance therapy following three-month induction with Avastin or Lucentis. Patients are getting induction with Avastin or Lucentis and then maintenance Macugen every 6 weeks for 48 weeks. Interim, 24-week data were presented on 83 patients at ARVO, and Dr. Tolentino said that the data showed that, after induction, there really is maintenance of vision with Macugen, "This supports the hypothesis that for initial disease, you need a pan isoform VEGF inhibitor, but for maintenance, you may not need as much."

In the real world how are patients treated? An expert said, "What's going on now clinically is that patients received 2-3-4 injections of Lucentis or Avastin and then are being observed with no maintenance until they re-ignite, heat up again, with monitoring with OCT and fluorescein angiography…We tell patients we are really good at starting these medications but really lousy at stopping them." Dr. Tolentino takes a different approach: "I give a pan VEGF inhibitor isoform to get patients to the best they can be. That generally takes 1-4 shots. Then, I maintain them with Macugen and give Lucentis or Avastin boosters as needed…But it is very hard to get Macugen paid for right now. Eyetech needs to do real trials on Macugen maintenance."

Another expert who was impressed with Dr. Tolentino's approach said he would use Macugen for:

1. Patients who had a recent stroke or MI.
2. Patients who have a stroke or MI while on either Avastin or Lucentis.
3. Possibly as maintenance therapy with Avastin or Lucentis. "If the company can hang around, Macugen will have a role, especially if they come out with microspheres that work for 6-12 months. And I think Macugen will be effective in diabetic retinopathy and RVO."

OTHERA PHARMACEUTICALS' OT-674/OT-551

A poster discussed the broad spectrum anti-angiogenic effect of OT-551 in inhibiting oxidative stress and pro-angiogenic growth factor-mediated angiogenesis in combination with anti-VEGF agents. The key points in the poster were:

- OT-551 is a novel, small molecule inhibitor that down-regulates pro-thrombotic states which are up-regulated by anti-VEGF and other anti-angiogenesis agents.
- The pro-angiogenic effects of different mediators was significantly ($p<.01$) inhibited by OT-551.

- OT-551 has broad potential efficacy against various stimuli and potential benefit alone or in combination with other single-mechanism-based anti-angiogenesis agents in the prevention and treatment of diabetic retinopathy, AMD, and other ocular disorders.
- In this poster, OT-551 was evaluated at doses of 30-800 µg in chorio allantoic membrane (CAM) in combination with Avastin or Lucentis.

Doctors asked about this agent were generally unfamiliar with it. Othera officials explained that:

➢ OT-551 gets to the back of the eye, as evidenced in radio-labeling studies.

➢ There is more additive effect with Lucentis than with Avastin because the molecular weight of Lucentis is smaller, and the larger Avastin molecule folds.

Additive Effect of OT-551

Treatment	No OT-551	OT-551 30 µg
VEGF + Lucentis 1 ng	18%	54%
VEGF + Lucentis 10 ng	33%	69%
VEGF + Lucentis 100 ng	53%	83%
VEGF	---	~ 36%
VEGF + Avastin 1 ng	37%	56%

➢ In a Phase I study of ~30 patients given topical administration, there were few adverse events – no irritation or redness.

- An official said, "In animals, at 10 times the dose, we still didn't see any side effects."
- When administered topically, the half-life in the blood is very short (minutes) vs. a long half-life (hours) in the eye. An official insisted, "There is no possibility of systemic effects."
- There is no contralateral effect.

➢ A Phase II study in cataract prevention is starting in post-vitrectomy patients.

- About 170,000 patients get vitrectomy each year. Typically, 100% of these patients get cataracts within two years of the procedures. This is the same cataract as in age-related cataracts.
- The trial will have more than 100 patients and run 18 months, with an interim look at 12 months.
- Othera is not seeking orphan designation. An official said the FDA "won't let us file for it."
- Two doses will be tested (high and low) vs. placebo.

➢ Three Phase II trials have started or are starting soon in AMD. No Phase I in AMD is needed, an official said.

- Wet AMD as an adjunct to standard-of-care (Lucentis).
- Dry AMD.
- A National Eye Institute-sponsored monotherapy trial that has already started in severe bilateral dry AMD. This is a 2-year study.

➢ When the company gets to Phase III, an FDA official indicated it can choose to do a two-arm trial as add-on therapy to Lucentis or as monotherapy vs. placebo. Either would be acceptable, though the official admitted that add-on-therapy would probably be easier to enroll. If Lucentis is the comparator, a third arm of the Othera drug alone would not be required.

➢ Othera is in preclinical development of topical and oral formulations for wet and dry AMD, but the topical is further along. The oral is another compound, not OT-551.

- When administered topically, there is considerable drug in the lens, even with the low dose.
- In dry AMD, Othera is looking at this as mono-therapy. Because it is a very powerful down-regulator of NFkB, it may have utility as both a preventive and a treatment.

Othera has no partners and is not in talks with anyone yet. It is a private company but is considering the option of going public. An official said, "Non-ophthalmic companies are more interested in this than other ophthalmic companies." J&J is an investor.

How would OT-551 be used? An official suggested it might be good for maintenance in AMD with Lucentis or Avastin in lieu of Macugen, "This might make Avastin or Lucentis safer." Data are expected at the International Society on Thrombosis and Haemostasis meeting in Geneva July 6-12."

REGENERON'S VEGF-Trap

The CLEAR-IT-I trial – a 6-week, single ascending dose study – found mean BCVA improved by ~4 letters and was then maintained, and the 4 mg dose showed a statistically significant reduction in retinal thickness which was described as "quite dramatic for such a small study." The drug was also well tolerated, with no ocular inflammation.

The results of the randomized, controlled, masked, 150-patient, Phase II CLEAR-IT-II were also presented at ARVO. This trial tested five doses of VEGF-Trap. The interim results showed:

- No drug-related serious adverse events, with the drug generally well tolerated.
- The trial met the primary endpoint of statistically significant reduction in retinal thickness, with all groups combined showing a 135 micron decrease from baseline ($p<.001$).
- A mean improvement in visual acuity from baseline of 5.9 letters ($p<.0001$).
- All but one patient maintained or improved vision at 12 weeks.

- There was no statistically significant difference across the five dose groups.

A Phase III trial is expected to start at the end of 2007. It will be a non-inferiority trial vs. Lucentis. That apparently was not mandated by the FDA but "strongly recommended." No other design details on that trial were available.

A poster at ARVO by Dr. Bjoern Bachmann of Germany reported on use of VEGF-Trap after keratoplasty. Dr. Bachmann said that VEGF-Trap doesn't shorten the waiting period before keratoplasty to allow inflammation to subside, but it does increase survival of the corneal transplant and modifies the kind of healing. He said VEGF-Trap is very potent, with systemic side effects – blood pressure and cardiac events – an issue, but he suggested it may be as good as optical agents for keratoplasty, though not as good for AMD, though Regeneron is focusing on AMD.

Another expert predicted VEGF-Trap can have a role but said it will need to have a non-inferiority trial – even if not for the FDA but to get any commercial use.

Another poster looked at inhibition of corneal angiogenesis with topical administration of VEGF-Trap after corneal suture surgery in 30 mice. The VEGF-Trap was administered TID as 4 mcL (in 3 concentrations: 1 mg/mL, 10 mg/mL, and 100 mg/mL) vs. control, for a cumulative dose of 12 mg/day, 120 mg/day, and 1200 mg/day, respectively. At 9 months the researchers found topical administration of VEGF-Trap inhibited corneal neovascularization and inflammation after suture injury. They said:

- Corneal neovascularization was reduced 60.1%, 87.7%, and 98.4% for the low, medium, and high doses, respectively.
- The treatment markedly reduced inflammation induced by corneal injury.
- No free VEGF-Trap was detected in serum.

ANTIBIOTICS

BAUSCH & LOMB'S SS-734

A poster reported on a 269-patient, multicenter, double-masked, parallel group, Phase II trial of this novel fluoroquinolone antibiotic, which B&L got from a Japanese company, SSP (now Hisamitsu Pharmaceutical Co.). With TID dosing, researchers indicated it is effective against bacterial conjunctivitis. A source commented, "It has wonderful potential, but the problem is even if they get this to market, can they sell it? They don't have the sales force of Alcon."

Adverse Events with SS-734

Adverse events	AUC_{50}	MIC_{90}
Infection	0.03	0.06
Pneumonia	0.06	0.12
Staph. aureus	0.13	0.25
S. epidermidis	0.06	0.5

INSPIRE'S AzaSite (azithromycin ophthalmic solution 1.0%)

With two well established fluoroquinolone antibiotics on the U.S. market – Alcon's Vigamox (moxifloxacin) and Allergan's Zymar (gatifloxacin) – is there a role for AzaSite, which was approved by the FDA just a week before ARVO? Inspire appeared to have been caught a little off guard with the approval since they had no information to give out at the booth.

Dr. Scott Schatz of Nova Southeastern University College of Optometry presented a study that suggested patients are less likely to get fungal contamination with Zymar 0.3% than Vigamox 0.5%.

Most doctors asked about AzaSite had not heard about it. A Florida doctor said, "Why would anyone use AzaSite when gatifloxacin and moxifloxacin are available?" Another doctor asked, "Why do we need this?"

THEA LABORATORIES' T-1225 (azithromycin ophthalmic solution 1.5%)

Researchers reported that this potential French competitor to Inspire's AzaSite (azithromycin 1.0%) was well tolerated in animals undergoing PRK and LASIK, with an evident antibiotic effect. They pointed out that T-1225 is oil-based, and AzaSite is water-based, and they suggested T-1225 could have a modulatory effect in corneal wound healing.

In another poster, Thea researchers reported on three BID doses given for 3 days: 0.5%, 1.0%, and 1.5% of T-1225. They found the 1.0% and 1.5% reached higher minimum inhibitory concentrations (MICs) than the 0.5% dose, with similar PK profiles, but the 1.5% dose had a higher AUC and lasted longer in the eye. How long the drug lasts in the eye is especially important in treating Chlamydia which needs 7-day antibiotic treatment, a researcher explained, adding that only the 1.5% dose provided this coverage.

Asked what the advantages of T-1225 are over AzaSite, he said, "T-1225 is stable at room temperature and at high temperatures, requiring no refrigeration, and the dose is based on kinetic studies, which Inspire didn't do."

CONTACT LENSES

Miscellaneous

- There were no data or information available at ARVO on Advanced Medical Optics' new contact lens solution, but experts were convinced that, like existing solutions, it will not kill *Acanthamoeba*.
- There was a rumor that Johnson & Johnson may be entering the contact lens solutions business with the purchase of a Japanese company. No details were available.

CORNEAL AND REFRACTIVE SURGERY

20/10 PERFECT VISION

Dr. Donald Tan of Singapore presented data on the use of 20/10's Femtec femtosecond laser (40 Hz prototype) in corneal transplants in 53 separate ablations in 13 corneas, using a procedure he has dubbed FLEK (femtosecond laser-assisted endothelial keratoplasty). He said he has developed algorithms and profiles for this procedure, using a 2-stage approach:

1. Vertical trephination – 7.5 mm diameter, laser ablation proceeds upward from the anterior chamber, with the aim to ablate up to 180 microns from Descemets membrane.
2. Lamellar ablation – 8.0 mm diameter, 150 microns from Descemets membrane.

Dr. Tan said various laser ablation parameters were tested – single, double, and triple passes for both vertical and horizontal cuts. He found:

- On his 1-4 stromal bed grading scale, a double pass provided the best stromal quality.
  - 1 pass did not get very high quality beds – not as good as a mechanical microkeratome cut. Mean grade 1.85.
  - 2 passes generally produced a smooth stromal bed surface that equaled or exceeded mechanical micro-keratome smoothness and which was very "peelable." Two passes were statistically significantly better ($p<.001$) than a single pass or a triple pass. Mean grade 3.0.
  - 3 passes were statistically better ($p<.001$) than one pass but inferior ($p>.05$) to two passes. Mean grade 2.58.
- Rim cut quality was comparable to a mechanical microkeratome.
- There was minimal morphological damage to the endothelium.

Dr. Tan concluded, "Microkeratome-assisted lamellar dissection with an ALTK unit is currently today's method of donor preparation for DSAEK. However rapid advances in femtosecond technology and improved ablation algorithms are redefining high quality stromal bed and rim cut qualities which are now equal to microkeratome-assisted dissection. Femtosecond ablation of 150 microns from Descemets membrane does not appear to alter or damage corneal endothelial morphology – but we are still testing it to see how close we can go. FLEK is the latest development in the evolution of endothelial keratoplasty."

Asked if there is a difference in the relative thickness of the cut at the center with FLEK vs. a microkeratome, Dr. Tan said, "We do see some differences…The periphery is thicker…All femtosecond lasers ablate from the anterior surface which is the reference point…However, I believe (20/10 Perfect Vision is) devising a different system where they will map the posterior corneal surface. Once you can use Descemets membrane as the reference point that might solve that issue… Certainly, we see much less variation with FLEK than a microkeratome."

DIABETIC MACULAR EDEMA (DME)

FDA requirements for Phase III trials

The FDA has required all DME trials to run for at least three years, but a year ago the FDA opened the door to a shorter timeframe. Dr. Wiley Chambers, deputy director for the FDA's division of Anti-Infective and Ophthalmology Products, explained that the 3-year rule was implemented after the DTTC (Diabetes Control and Complications) trial showed that the curves between insulin and placebo initially appeared worse (went in the wrong direction) for insulin but at about 1.5 years, the curves began to converge, and at three years the curves reversed, with insulin superior to placebo, "So, if you don't look long enough, you would draw the wrong conclusion."

Dr. Chambers said two-year data from a pivotal trial would be sufficient if both of the following two analyses are done and statistically significant, but two years is the shortest possible time for a DME trial:

1. **Analysis 1.** A comparison of the investigational drug to the control from baseline to two years.
2. **Analysis 2.** An analysis using the 1.5 year time point as the baseline. That is, the investigational drug has to be statistically better than the control over the last six months of the trial (from 18 months to 24 months). This may be a difficult hurdle, Dr. Chambers said, pointing out that 1.5 years to 2 years may not be enough time.

Thus, if an investigational drug was superior to the control from Day 1 to the end of the trial, two-year data would not be a problem for FDA approval.

SURMODICS' I-vation triamcinolone implant

I-vation is a non-ferrous metal MP35N alloy coil coated with a durable polymer (BRAVO, the same polymer used on J&J's Cypher stents) that is implanted into the eye through the conjunctiva and is anchored to the eye wall without sutures. It is designed to elute triamcinolone for ≤2 years.

At the American Academy of Ophthalmology meeting in November 2006, SurModics presented 6-month data from a three-year Phase I proof-of-concept study in 31 patients with DME, using a first-generation device and delivery system, testing two doses: low (1 mg/day) and high (3 mg/day). At ARVO, the company presented 9-month efficacy data on 27 patients (the others hadn't reached 9 months yet) and 12-month safety data from this same trial. At the start of the study, 23 patients were phakic and 8 were pseudophakic.

Among the Phase I findings were:

- **Overall.** Researchers concluded that the procedure was "routine" and that both the slow and fast formulations were well tolerated. They also found that there was an efficacy "trend" compatible with the drug elution curve at 9-months post-implant, with 85.2% of eyes stabilized or improved from baseline.
- **Cataracts.** Three of the 23 patients who were phakic at the beginning of the study developed cataracts. One was at 9 months, and two were between 9 and 12 months. The official said, "I don't think we are seeing any increase (in cataracts) beyond what we would expect." She pointed out that, this is in contrast to B&L's Retisert (which elutes fluocinolone acetonide), where 100% patients develop cataracts.
- **Explants.** 12 patients had the device removed.
  - 2 of these discontinued the study, one at ~30 days and another at ~6 months. In the first case, the cap was close to the surface. A SurModics official said, "There were no patient complaints or adverse events, but the physician thought that to avoid the risk of infection, he wanted to take it out." In the other case, "the conjunctiva was very thin, and that was one reason for our design change."
  - 10 had the implant removed and then another device implanted because, based on OCT readings, it was determined that they needed more drug. One of these had the second device taken out and replaced with a third device.
- **Glaucoma.** IOP increases were described as a "known, common side effect with triamcinolone, and all patients experienced a 4 mmHg change from baseline over the 9-month treatment period: from an average of 13.7 mmHg at baseline to 17.3 mmHg for the slow release formulation and 18.0 mmHg for the fast release formulation. No patients had sustained, uncontrollable IOPs.
  - 10 patients had elevated (spikes in) IOP. Two of these were determined not to be drug-related, 2 were related to the procedure, and 6 were related to the drug.
  - 4 of these patients had IOP increases >24 mmHg. All were treatable and responsive to drug therapy.
  - No patients required filtration surgery, and there was no optic nerve involvement in any of the patients.
- **Adverse events.**

12-Month Adverse Events in I-vation Phase I Trial

Measurement	Related to medication	Related to procedure
Anterior chamber inflammation	0	12.9%
Conjunctival erosion	3.2%	6.5%
Conjunctival hemorrhage	0	90.3%
Conjunctival hyperemia	3.2%	19.4%
Contusion	0	16.1%
Corneal edema	0	3.2%
Corneal epithelium defect	0	3.2%
Episcleral hyperemia	0	3.2%
Eyelid edema	0	9.7%
Eye irritation	0	6.5%
Eye pain	0	12.9%
Foreign body sensation	0	6.5%
Increased IOP ≥10 mmHg from baseline	25.8%	6.5%
Increased CLGP score >1 from baseline	35.5%	0
Vitreous hemorrhage	0	3.2%
Serious adverse events	0	N/A

- **Case study** – on a 56-year-old pseudophakic white female with bilateral DME – was presented on the Phase I poster.

Case Study Results

Time period	BCVA	Letters	Retina thickness	IOP	Adverse events
Pre-op	**50**	**64**	**255**	**15**	**---**
3 months	**160**	**42**	**173**	**19**	**PCO**
6 months	**32**	**77**	**N/A**	**17**	**Nd:YAG**
9 months	**25**	**81**	**152**	**21**	**---**

- **Best corrected visual acuity (BCVA).** At 9 months, 33% of patients achieved ≥20/40 vs. 18.5% at baseline. Mean letters achieved was 59.7 vs. 58.8 at baseline. This was described as "a trend that points to efficacy." A SurModics official pointed out that the BCVA data in Phase I were collected just before two of the patients who developed cataracts had their cataract surgery, so the numbers might have been affected by that.
- **Central corneal thickness.** Researchers reported that the results of fundus photography, fluorescein angiography, and OCT indicated the disease was arrested in the "majority" of patients. On average, near center thickness changed -102.1 μ from baseline, with a -156.5 μ change with the slow dose, and a -51.6 μ change for the fast dose.

9-Month Efficacy Results in I-vation Phase I Trial

Time period	Mean central corneal thickness		Mean IOP		BCVA			
	Slow formulation	Fast formulation	Slow formulation	Fast formulation	20/40	20/50 - 20/80	20/100 - 20/200	Worse than 20/200
Baseline	550.2	365.7	13.7	13.7	18.5%	51.9%	25.9%	3.7%
3 months	396.4	233.5	17.0	17.8	33.3%	51.9%	11.1%	3.7%
6 months	363.8	235.1	16.1	16.3	44.4%	40.7%	11.1%	3.7%
9 months	393.7	314.1	17.3	18.0	33.3%	33.3%	25.9%	7.4%

Phase II. The next step is a 1-year, randomized, prospective, multicenter, masked Phase II trial in 120 DME patients. This trial is not due to start until the end of 2007 because SurModics is "currently working on more formulation development," an official said, adding, "We are reformulating doses…We will have three doses, and that's why we are waiting to start the Phase II trial …We need *in vitro* data to make a final selection."

The trial will not have a placebo arm. A SurModics official said, "Our suggestion to the FDA is that we will demonstrate a difference between the doses, and that will be attributed to the drug."

This trial only needs to be one year because it is a dose-finding study. It will use a second-generation device and a new delivery system, and patients will not be permitted to get more than one implant (no re-implants). The Phase II trial will compare three doses of triamcinolone – very low, medium, and high. The high dose will be a 925 µg load in a 12-month implant, the intermediate dose will be 500 µg, and the low dose will be 100 µg. There is no control, but the very low dose is in lieu of a control. The protocol for this trial was submitted to the FDA, which reportedly said, "Show us the data," indicating the trial can proceed as designed but not making any commitments.

- ***New device:***
  - **Easier to implant.** The first turn was described as "not natural," and this design is supposed to fix that.
  - **Positioning.** The device will now sit "more flush to the sclera."
  - **Comparable efficacy/safety.** A SurModics official said, "All our bench data and rabbit data show the results in the study should not change (by using this device instead of the first-generation device)."
  - **No point on the end.** Instead of using the end of the implant to insert the implant, doctors will use a 25 gauge needle to start the sclerotomy.
- ***New delivery system:*** This was described as a "great implantation tool" and "very cool." It is scheduled to be released in early 2008. It has a finger-activator, a self-retractor. It is the same length as the first-generation delivery device, but it has increased surface area, has a thicker polymer coating, and has fewer sharp edges (and no notches). The cap also has been modified to allow the device to fit more flush with the sclera.

For **Phase III**, a SurModics official said the FDA will require 3-year data on the patients, but not a three-year implant. I-vation is classified by the FDA as a drug, not a device. Asked how long the final commercial product is likely to work, she said, "We anticipate at this point a one- to two-year treatment."

Other SurModics devices. A SurModics official said the DME trials will be a springboard for delivery of other drugs (but so far no VEGF) on this and other related platforms. She said the company has 3-month data in rabbits for delivery of model proteins. Several other platforms are in development. None of these have gone into the clinic yet, and none are expected to begin human clinical trials in 2007. They are:

- Biodegradable polysaccharide filament for protein delivery (IgG, FAB, etc.).
- Subretinal, nano-engineered filament with a durable BRAVO coating.
- Coil with a biodegradable coating "for protein delivery, for delivery of large molecules, different drugs, hydrophobic and hydrophilic drugs."

Partners. SurModics is looking for partners for these and other projects. An official said, "Our business model is to develop the technology and partner with companies developing novel compounds (by his definition, Lucentis and Avastin are novel compounds)…We have six feasibility programs underway, and three are with top 10 pharmas." Another SurModics official said, "We are prepared to go into Phase II (with the triamcinolone-eluting, durable polymer-coated coil), but our preference is to partner with someone to develop this…We don't ever want to be competing with our customers…We are developing other drugs potentially for the platform…We definitely gained the safety experience enough to try the platform…and that was a large amount of the justification for taking this as far as we have ourselves. If we work with a partner drug, it would be their Phase I, Phase II, and Phase III trials. From the beginning, they would take control of their clinical development, in partnership with us…We have the objective that by the end of our fiscal year (the end of September 2007), that our ophthalmology group will sign a license with a partner. We have an objective, and we feel we are on track to meet that objective."

SurModics officials were careful to characterize the proteins their devices are designed to deliver in rather generic ways – as IgG or FAB. They specifically avoided any reference to Genentech's Lucentis and Avastin or any other VEGF inhibitor. One official said, "All the proteins we have worked with so far are IgG and FAB."

Other issues. A rat study by researchers at Indiana University and the National Institutes of Health found that there appears to be a maximum efficacious dose of triamcinolone – ~40 mg/mL in mice or ~25 mg/mL in humans. A researcher said, "People have been using triamcinolone off-label without good data on dose, just assuming: 'If a little is good, more is better.' But that doesn't apply to triamcinolone. Higher doses (>25 mg/mL) can aggravate pre-existing, deleterious effects, such as causing CNV to worsen, inducing retinal NV, or retinal choroidal anastamoses."

Asked what the implications of this study are for I-vation, the researcher said, "We need to know the maximum concentration in the eye (and the gradient area) because triamcinolone doesn't disperse. It is a molecule in a suspension that remains a suspended molecule. It doesn't disperse well in water." He

also said NIH tried triamcinolone pellets in the past, "They worked, but you had to be careful with dosing. Intravitreal triamcinolone can elicit inhibition or paradoxically augmentation of CNV in a rat."

ALLERGAN'S Posurdex (dexamethasone posterior-segment sustained-release delivery)

While not directly related to Posurdex, a Korean study of dexamethasone in cultured rat retinal cells has some implications for Posurdex for RVO and DME. The researchers reported that dexamethasone is not highly cytotoxic to retinal cells, despite having potent glucocorticoid effects. They concluded that a slow-release dexamethasone device would be preferable in terms of long-term bioavailability of glucocorticoid.

Asked how he would choose between Avastin and a dexamethasone implant, a Florida researcher said the choice would be based on age, "For patients between 20 and 50, I'd watch them. Older patients would get Avastin – or a dexamethasone implant if they need frequent re-injections of Avastin. Over age 60, I would consider Kenalog (Bristol-Myers Squibb, triamcinolone)."

Asked how he would choose between Posurdex and SurModics' I-vation, an expert suggested I-vation might be more appealing, "It seems drastic to do a cut-down and beveled incision in the office and use a 23 gauge implant (Posurdex). Posurdex still requires a cut-down, so it is not comfortable for the patient…but several studies have found that Avastin works in RVO."

Comparison of I-vation and Posurdex

Issue	Advantages to I-vation	Advantages to Posurdex
Speed of effect	Slow	Quick
Length of effect	<1 year	3-6 months
Where administered	OR	Doctor's office
Risk of infection	Less with insertion in OR and with flap covering conjunctival wound	Greater with uncovered 25 gauge hole
Cutting of conjunctiva	More	Less

ALIMERA SCIENCES/pSIVIDA'S Medidur

This small, intravitreal device (3 mm long x 0.37 mm diameter) is delivered with a 25 gauge injector system. It delivers fluocinolone acetonide (a corticosteroid) to the retina at a dose of either 0.2 µg or 0.5 µg per day for ≤3 years. It can be implanted in the office and requires no sutures. A three-year, 900-patient, randomized, masked, multicenter (U.S., Europe, Canada, and India) Phase III trial, FAME, began in September 2005. In April 2007, the company announced that >500 patients had been enrolled so far. Pfizer recently agreed to pay pSivida up to $155 million for development related to different ophthalmic applications of the Medidur technology.

Overview

A retina specialist familiar with all of these products said Posurdex has a more rapid effect early on but only lasts 3-6 months. In contrast, I-vation's effect is much slower, but lasts longer, "It really is a sustained slow release." Posurdex can be administered in a doctor's office, and this source said that is a big advantage, "With I-vation you have to go to the operating room (OR), but that could mean less risk of infection because I-vation is being done in a sterile OR." However, this expert didn't think doctors would want to take patients to the OR, which would give Posurdex an advantage, though he pointed out, "If I-vation really works for a year, then it might be worth it. I-vation requires cutting the conjunctiva, but there is a flap that covers the wound."

He also is "underwhelmed" with Medidur, saying, "I-vation works better than Medidur."

VEGF Inhibitors for DME

Dr. Ingrid Scott of Penn State College of Medicine reviewed the status of VEGF antagonists for DME. She said there is a strong basic science rationale for studying the safety and efficacy of anti-VEGF as a treatment for DME.

- **Macugen.** A double-masked, multicenter, randomized, 36-week Phase II trial of Macugen found a statistically significant benefit to the 0.3 mg dose vs. sham in terms of median visual acuity, percent of patients gaining ≥10 letters, and patients with decrease of retinal thickness. But the study did not address longer-term effects (≥3 years), and the sham group had fewer patients with a laser treatment.
- **Lucentis.**
  - A single center, open-label, dose-escalation, pilot study of 10 patients getting three monthly injections (half at 0.3 mg and half at 0.5 mg) found a substantial decrease in retinal thickness, 4 patients gained ≥15 letters of vision, and 5 gained ≥10 letters.
  - A Phase III trial of Avastin, funded by the National Eye Institute, is ongoing.
  - The READ study looked at 12-month outcomes in 18 patients.
  - READ-II is ongoing, with 60% of patients enrolled so far. It compares Lucentis 0.5 mg vs. Lucentis + laser vs. Lilly's Arxxant (ruboxistaurin mesylate), a protein kinase C-β (PKC-β) inhibitor, in 126 patients. In August 2006 the FDA issued an approvable letter for Arxxant for diabetic retinopathy, asking for more data.
- **Avastin.** A Phase III trial of Avastin, funded by the National Eye Institute, is ongoing. The primary endpoint is retinal thickening on OCT (the proportion of eyes with ≥50% reduction in center subfield thickening or a reduction to <250 microns at 12 weeks).

- **Lucentis or Avastin.** In a Pan American study, 88 patients were given either Avastin or Lucentis, with 20% getting a second injection and 8% a third injection. Mean BCVA improved from logMAR 0.897 at baseline to 0.6 at the end of the study (p<.0001), with 55% improved 2 lines of vision, 41% stable, and 4% having decreased vision.

DRY EYE

ALACRITY BIOSCIENCES' doxycycline drops

A Phase I study in 30 patients found no statistically significant change in central corneal staining at Day 14 or Day 28 (p=0.099) vs. vehicle, but there was a statistically significant improvement in the signs and symptoms of dry eye.

INSPIRE'S Prolacria (diquafosol tetrasodium ophthalmic solution 2%)

Twice the FDA failed to approve diquafosol, instead issuing approvable letters both times. In the last letter, the company said the FDA wrote: "The submitted clinical studies fail to demonstrate adequate replication of results for the efficacy endpoints and therefore are insufficient to establish efficacy. Based on our review of the submitted data, consistent findings of corneal clearing need to be demonstrated to support the efficacy of the drug product."

Inspire officials insisted they have not given up on diquafosol, and they are hoping that new data on central corneal staining alone will be sufficient. An official said, "We are in discussion with the FDA on endpoints for another Phase III trial." The company wants clear central cornea as the primary endpoint; the FDA issue is the clinical benefit of clearing the central cornea.

Inspire reportedly doesn't want to have to show an improvement in visual acuity, but a poster at ARVO suggested there is an improvement in visual acuity with diquafosol. The study was a post hoc re-analysis of completed diquafosol trials.

Post Hoc Analysis of Diquafosol Trials

Trial	Weeks	Placebo	Diquafosol	p-value
Complete Central Clearing				
Study 03-105	6	39%	51%	0.029
Study 03-108	4	71%	81%	Nss, 0.052
Study 03-109	6	51%	66%	<.001
Visual Acuity (0-3 scale)				
Studies 03-104 and 03-105	12	N/A	0 = 0.09 3 = 0.25	<.001

Selenoprotein-P

Japanese researchers reported that selenoprotein-P – one of the essential components of autologous serum tears – is a new candidate for treatment of dry eye, based on a rat study. No commercial involvement was listed.

GLAUCOMA

ALLERGAN'S memantine for glaucoma prevention

Allergan conducted two Phase III trials simultaneously of memantine as a glaucoma neuroprotective, trying to prove that memantine preserves visual function in glaucoma patients. The company announced that the first trial failed to meet the primary endpoint – a functional measure of vision – but on a secondary functional measure memantine did show a statistically significant benefit ***at the high dose***. Allergan reportedly is asking the FDA to allow it to change the primary endpoint in the second Phase III trial, which is completed but has not yet been unblinded.

Will the FDA allow a primary endpoint to be changed after a trial, any trial, is fully enrolled or completed if it has not been unblinded? The FDA's Dr. Chambers said, "Changes to the primary endpoint are supposed to be made before the trial ends (before enrollment is complete or before the blind is broken) ***and*** because there are new data suggesting a reason for the change – some new information came out that the company didn't have at the time the trial was started."

Dr. Chambers said there is dissension within the FDA over this issue, but his personal opinion is that it is acceptable to change the primary endpoint after the trial is finished, provided there are new data creating a reason for the change. He said, "It depends on when you change the endpoint and who at the FDA evaluates it. There is a difference of opinion within the FDA on whether this should be allowed."

Changing the primary endpoint, Dr. Chambers explained, does not necessarily result in a statistical penalty. He said that a statistical penalty is only applied if the data are unblinded or an interim look is taken at the data, "There is no statistical penalty if you haven't analyzed anything." **Thus, it would appear that the FDA is likely to let Allergan change the primary endpoint in the second Phase III memantine trial and to do so without a statistical penalty.**

Prostaglandins

Recently, Alcon's Travatan (travoprost) has picked up some market share in the prostaglandin marketing wars. Sources at ARVO attributed this to the introduction of Travatan-Z, which contains no BAK preservative (the original Travatan did have BAK). Alcon reportedly has been marketing Travatan-Z by focusing on the lack of BAK and pointing out that Pfizer's Xalatan (latanoprost) does contain BAK. Experts agreed the difference is minor, but they said it gives Alcon a point of differentiation that may resonate with some doctors.

A Pfizer poster at ARVO reported on a monkey study that found no difference in corneal safety between topical ocular products that do [Xalatan and Alcon's Patanol (olopatadine)] and don't (Travatan-Z) contain BAK.

A rabbit study reported in a poster at ARVO found that a single oral dose of memantine – as measured by fundus photography and sweep visual evoked potential (SVEP), which is used to measure sight in infants – is neuroprotective following acute IOP elevation. SVEP was down 24% in placebo vs. up 3% with memantine.

An Israeli researcher doubted that memantine will prove effective in glaucoma protection, adding, "If it did block sufficiently, you would get side effects. Merck's MK-801 was an excellent neuroprotectant in cells and animals, but in a Phase I study it was psychotropic because it blocked too efficiently."

EyeLight's Excimer Laser Trabeculotomy (ELT)

Dr. Michael Berlin reported on this LASIK of the trabecular meshwork that eliminated the known pathology of glaucoma outflow obstruction. He said the procedure restores normal flow using the eye's own mechanisms. A special, 308 nm excimer laser from Coherent is used, with a fiber optic delivery system. More than 2,200 patients have been treated in Europe, but it is not yet available in the U.S. EyeLight plans to bring it to the U.S. (Coherent OEMs to them) with a second-generation laser in about 24 months, applying for a 510(k). He said the company is waiting for financing to finish the second-generation development.

Miscellaneous

Abbott's Humira (adalimumab)

A poster by researchers from Louisiana, Texas, and Brazil reported on intravitreal use of Humira in rabbits as a possible steroid-sparing agent for uveitis. In this investigator-initiated study, they found escalating doses of Humira had no drug-associated toxicity up to 500 μg.

Alcon's Retaane (anecortave)

Alcon reportedly is "keeping its options open" and watching research into the use of Retaane in diabetic retinopathy and retinopathy of prematurity (ROP). Early work by researchers at Vanderbilt University suggest Retaane may be useful in those disorders.

Amgen's Epogen (erythropoetin alfa)

An investigator-initiated study by researchers at Columbia and Yale looked at the use of intravitreal injections of EPO as a neuroprotective agent for neurodegenerative diseases (retinal ischemia-profusion injury, glaucoma, etc.). In rabbits, they found that injections don't cause negative effects on IOP, retinal morphology, or retinal function at doses up to 1600U. There was no evidence of retinal neorevascularization. A researcher said, "I think monthly injections might be useful as a last line of treatment for patients who don't respond to oral agents."

Other anti-angiogenic agents in development that experts mentioned include:

- siRNA – both Allergan and Acuity are in early trials with an agent in this category.
- GenVec has a propriety adenovector, to deliver the PEDF gene.
- Dr. Campochiaro suggested two other VEGF targets: blocking either stromal derived factor -1 (SDF-1) or CXCR4, but he didn't point to any specific agents in development.

QLT's QLT-0447

QLT is investigating this agent for CNV. In rats, a therapeutic concentration was found that will be used for development of ocular formulations.

Wyeth's Rapamune (rapamycin)

University of Florida researchers suggested that rapamycin may have utility in retinitis pigmentosa (RP), based on an investigator-led mouse study. They said, "We think it works by inducing autophagy." They found the best dose in RP was once-weekly. Next, they plan to repeat the study in other animal models and other disease types, including AMD.

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