Trends-in-Medicine

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By Lynne Peterson

SUMMARY

For AMD: Bristol-Myers Squibb's Kenalog is getting more and more attention. Doctors predicted EyeTech's EYE001 is the one to watch, but there was no new data on this. Genentech's anti-VEGF, Lucentis, got a lukewarm reception. The Phase III trial of Alcon's anecortave is enrolling slowly, but the dropout rate is low. Meanwhile QLT acts like these Visudyne competitors don't exist.
For uveitis: Hopes are fading for B&L's Retisert back-of-the-eye implant.
For dry eye: Allergan's Restasis is off to a strong start, but Alcon has 15(S)-HETE in development.
For glaucoma: The marketing wars continue.

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Following is a look at some select topics, drugs, and devices discussed or presented at this meeting for ARMD, DME/uveitis, glaucoma, dry eye, refractive surgery. In addition, doctors were questioned about the outlook for various products.

AGE-RELATED MACULAR DEGENERATION (ARMD)

A variety of agents are in development to compete with QLT Therapeutics' Visudyne (verteporfrin). A speaker commented, "We can say VEGF is a critical stimulator for CNV, and whatever inhibits VEGF will be a good strategy, so it comes down to the delivery mode and safety…So, if it can be delivered in a less invasive method and has good safety, it will be the one used. But all VEGFs are good approaches."

Interestingly, the ApoE4 allele that is a negative predictor for Alzheimer's Disease appears to be protective for AMD.

ALCON'S Anecortave – Slow going with the Phase III anecortave trial, but the Dropout rate is low.

A speaker reviewed the one-year data from the 98-03 anecortave trial that was presented at the Retina Society meeting last Fall. He addressed a question raised at that meeting: "The reason 15 mg was better than 30 mg could be that we reached the peak of the dose response curve with 15 mg, or the delivery system may be delivering the drug in such a way that you get more effective penetration with 15 mg than 30 mg."

The Phase III trial head-to-head non-inferiority trial comparing a 15 mg dose of anecortave with Visudyne does not appear to have the same problem with dropouts that 98-03 had. A company official confirmed that the drop-out rate is <5%. This trial is still enrolling. Alcon recently announced that the trial would take longer than expected, and an official here explained this was because the trial is enrolling slower than expected. The official and other investigators explained this is due to several reasons, including:

- *Strict protocol.* Sources believe this is the key reason for slow enrollment, but they said this is not unique to anecortave. They described the protocol as "very, very strict" and probably not real-world.
- *Patient fear of the cannula.* One researcher said, "When patients see the cannula, they don't want to participate in the trial."

Questions have been raised about the blinding of the Phase III trial. Over the past few months, several investigators have commented that they could tell which patients have gotten Anecortave. Retina specialists speculated that this might be due to:

- *Good results*, which wouldn't affect treatment but could, affect patient response.
- *Hypofluorescence* on the angiogram in the treated area of PDT. This is a defect that retina specialists said is associated with PDT, but not anecortave, so when they see it, they know the patient is getting PDT.

Two other anecortave studies also are currently enrolling: one in Europe and one in South America. Both compare 15 mg anecortave to placebo. Another trial, looking at anecortave to prevent AMD in high risk fellow eyes, is due to begin later this year in the U.S.

Alcon also is working on a new delivery device for anecortave. A company researcher presented preclinical data on a new transscleral device for delivering anecortave directly to the eye to treat AMD. The device, which is now in primate studies, looks somewhat like a scleral buckle with a round tablet (diameter 5 mm) on the underside of one tip. It is made out of a soft, flexible silicone. A researcher said, "The advantage of this is that it is unidirectional, meaning the drug doesn't diffuse into the orbit as an injection would, so it is more efficient use of the drug pellet."

In preclinical studies AL-4940 and its active metabolite, AL-3789, were used, mixed with excipients. The researcher said both AL-4940 and AL-3789 are equally effective at inhibiting angiogenesis. PK studies showed the device can deliver AL-4940 for at least two years. Retinal levels of the drug were 21.3 µM at one week, declining to 0.1 µM at six weeks, remaining there through two years. The tablet/drug is dispensed to an area about 10 mm in diameter around the tablet; 180° away, there is little drug distribution.

In rabbits, the device was successfully implanted for six months, retrieved and another device reimplanted in the same place. No toxicities related to the implant were observed, no impact on body weight, IOP or corneal thickness. In a drug core analysis, the tablets were weighed before implantation and again on removal. For this analysis, researchers concluded that 20% of the drug was used in the first six months, which they said would project out to 100% at ~2.5 years.

The initial monkey studies in 14 animals tested F, H, L and U shaped devices. The H-shaped drugs have room for more drug, and the U shaped device can be used for either eye.

The devices were implanted without stitches, though a researcher said stitches may be used in the future, "We purposely did not place sutures. We feel the importance of this device is its safety, and once localized it will fibrose in place. Putting in a suture is easy, and we may need to do that to stabilize it…And one of the reasons we have not gone to sutures is we want to make the surgical technique so brief and simple that it is not much different than giving an injection – so you can put these things in very quickly. Using a suture would double the time."

In Study A, the F and L shaped devices took an average of 9 minutes to implant. A researcher said removal is quite easy. There were several adverse events, including two mild extraocular hemorrhages, one RPE, one choroidal thickening, one CME, etc.

In the next study, Study B, nine devices were implanted, with the average implant time two minutes. All the devices migrated slightly inferiorally. There were two mild extraocular hemorrhages (with no clinical consequences) and transient retinal striae but no PRE, no corneal thickening or CME. A researcher said, "Device design is critical…We are now testing another device to address the remaining issues from these two studies…Device B clearly had fewer complications…The future design should minimize migration."

BRISTOL-MYERS SQUIBB'S Kenalog (triamcinolone) – More and more interest.

Intravitreal injection of Kenalog continues to get attention for a variety of eye conditions, and many retinal specialists said they are doing it now, outside of trials. The major concern has been the incidence of endophthalmitis. A researcher suggested the problem may be the vehicle mix. His study found that shaking the bottle before drawing the drug into the needle lowered the incidence of endophthalmitis, and he suggested that the incidence of endophthalmitis may increase when the bottle settles and too much vehicle is administered.

Another study found non-infectious endophthalmitis occurred with intravitreal Kenalog injections in 7 of the first 104 patients (6.7%). All had painless visual loss but significant floaters and vision disruption. Some had a foreign body sensation but no pain or ache, and all cases occurred within two weeks of injection. All seven patients were treated, and none had permanent visual loss as a result of the endophthalmitis. Researchers concluded, "We feel it is probably a toxic reaction to the drug or the vehicle of the drug, perhaps an allergic response…We sent back all of our stock of Kenalog for new medication, and the incidence has been much lower with the new stock (<1%)."

Other researchers presented a 115-patient trial of Kenalog in occult patients ineligible for PDT which found: IVTA may increase visual acuity during the first three months after injection. Patients with an increase in visual acuity after the first injection may show a re-increase in visual acuity after repeated injections. Predictive factors for an increase in visual acuity with Kenalog may be pre-injection visual acuity and the

type of AMD. Yet, there are several unanswered questions about Kenalog, including: best dosage, which AMD indication, how often it must be re-injected, and possible side effects other than the observed ocular hypertension, cataracts and post-operative infectious endophthalmitis. An Australian researcher in the audience commented, "We did (Kenalog) studies, and I still think we need better evidence to recommend its use in AMD. I think it does improve vision in some patients, but we were impressed with the effect on macular edema...and it could be the vision improvement is due to drying out of macular edema, so the long-term outcomes may not be that beneficial."

A retrospective study looked at 14 patients getting intravitreal Kenalog plus PDT. It did not appear that the combination added much.

A researcher presented data on subretinal administration of Kenalog in the first nine patients in a compassionate use study. He said, "Subretinal administration may be better than intravitreal administration." A novel device by Innorx was used to administer the Kenalog, and the researcher said this device allows a smaller sclerotomy and smaller retinotomy than the B&L device normally used.

A study of intravitreal Kenalog in non-infectious uveitis in 20 eyes found improvement in edema in 75% of patients, statistically significant improvement in visual acuity at one month but not at 25 weeks (p-.06). Cataract progression occurred in 20% of cases, but the researcher said these were pre-existing cataracts. One patient had a retinal detachment. Mean IOP went up significantly at one month but was transient. The researcher concluded: Kenalog is effective for CME in patients with non-infectious uveitis refractory to other treatments…but we don't now the place of this procedure yet. We need more studies."

A retinal specialist said, "Wer'e getting really good results with Intravitreal Kenalog for CRVO, edema and DME, but just so-so results in AMD."

GENENTECH'S LUCENTIS (RHUFABV2) – Is the excitement cooling?

There were several presentations on DNA's VEGF in ARMD. Lucentis definitely did not get the warm reception at ARVO that it got at the Retina Society meeting last fall.

Dose escalation safety study. In this 20-week, open label, study the dose was escalated from 300 µg to either 1 mg or 2 mg. The 29 patients were not well balanced in terms of baseline vision and the arms small (9-10 patients), so the speaker warned against drawing efficacy conclusions. The most common ocular adverse events were: transient intraocular inflammation in <2% of patients and some injection site erythema, which was described as typical for an ocular injection. There was no endophthalmitis and no antibody formation, using a Genentech assay. Researchers concluded:

a. Lucentis was well tolerated at a dose up to 2 mg when given every two weeks.
b. Inflammatory response, which had limited the dose to 500 µg in previous studies, was not limiting up to a dose of 2 mg when the dose was titrated.
c. Patients in all three-drug arms demonstrated an increase of 12-14 letters, on average.
d. There was biologic activity in a range of lesions.

A researcher was asked which dosing regimen is better – every two weeks or once every four weeks. The researcher responded, "It was not pushed more frequently than every two weeks or longer than every four weeks. The study was not designed to tell the difference (between these dosing regimens), and the groups were too small to see if there is a difference. But, perhaps more frequent dosing is not deleterious and could get lesions under control, but you can't draw that conclusion from this study…When a patient responds to this, and we stop the drug, and then they relapse, and we give it again, and they improve -- that is a pretty good indication of a treatment effect…Over six months, 12 have needed retreatment, but it is highly variable at what stage. Some needed retreatment in two months and some not until six months out."

Six-month results from an open-label randomized Phase II trial. This open-label, randomized, controlled study had a total of 64 patients with three arms: usual care, 300µg monthly, or 500µg monthly. Eligible patients were enrolled into three strata: (a) minimally classic CNV (b) predominantly classic, or c) an active lesion after treatment with PDT. The three-month results were presented at the Retina Society meeting in October 2002, and six-month data on 21 of these patients from one of the eight sites was presented at ARVO. Not all the patients completed the full six-months even at this one site, reportedly because "they wanted to go south to escape the Boston winter" – so only 21 of 26 patients at the site were included in the analysis A Genentech official said the full six-month data from this trial will be presented at the American Society of Retina Specialists meeting in New York in August 16-20, 2003.

The conclusion and findings reported at ARVO were that:

- Lucentis is well tolerated.
- There has been one case of a CRVO, not previously reported, plus two cases of endophthalmitis, both of which were previously reported. The CRVO patient initially improved with Lucentis, then had the vision deteriorate substantially after the CRVO developed. Lucentis was stopped, and vision returned to the early treatment level (which was above baseline). Lucentis was not re-tried in this patient.
- The half-life is 3.5 days.

- So far, there have been no cases without a biologic response to Lucentis. The presenter said, "I've seen a couple of eyes with less response, but in virtually all eyes we've seen at least some reduction in fluid."
- There were no sham injections in the control group.
- There is some antibody formation, but no negative effects have been reported from this.
- It is unclear how long patients will have to be treated with Lucentis.

RhuFAB-V2 Phase I/II Results

Vision Loss £ 3 lines	Control n=11	rhuFAB 300 mg n=25	rhuFAB 500 mg n=28
3-Month Results			
Visual acuity at day 98	5.1*	+8.8	+9.1
Loss of ≤15 letters	20%	8%	4%
No change or an increase of ≤ 15 letters	80%	92%	96%
Increase of ≥ 15 letters	0	32%	21%
≥3 line gain	0	32%	21%
2 line gain	30%	68%	64%
Any gain	30%	80%	86%
Change in leakage	-.02	-2.44	-1.59
Subretinal leakage	.54	-2.63	-.7
6-Month Results (on a subset of patients)			
Number	5	8 of 11	8 of 10
Visual acuity at 210 days	-1.4%	+6.5%	+13.5%
Loss of ≤15 letters	---	12%	0
No change or an increase of ≤ 15 letters	---	88%	100%
Increase of ≥ 15 letters	0	32%	21%
≥3 line gain	---	50%	38%
2 line gain	---	50%	50%
Any gain	---	75%	100%

** Revised downward from original -4.9% reported*

Ongoing trials include:

- Phase III trial in occult AMD. This trial is testing 300 µg and 500 µg dose, given every 28 days. An official indicated that, like anecortave, Lucentis enrollment may take longer than previously expected.
- A Phase I trial of the combination of Visudyne and Lucentis.

Indocyanine Green-Enhanced Photodiode Therapy

This is now being referred to as IMP instead of I-PDT. A Venezuelan doctor said, "We use Visudyne first line at our clinic but have been looking for something less expensive for patients who can't afford PDT with Visudyne."

This researcher did a prospective study of 24 eyes in 18 patients, comparing IMP alone to IMP+triamcinolone acetonide (TA). An 810 nm diode laser and Akorn's indo-cyanine green (ICG) were used, with the 2.0 mg/kg of ICG divided into two boluses, given 30 minutes apart. Light was applied two minutes after the second bolus. Mean follow-up was 6.5 months. The most common complication was minimal discomfort during the procedure; there was no IOP elevation >20 mmHg. The variable visual acuity between the two groups was not statistically significant, but there was a trend (p=.05) in favor on IMP+TA. Perhaps the biggest limitation of this trial was the failure to have a TA-only arm.

QLT THERAPEUTICS' Visudyne (verteprofrin) – Ignoring the competition nipping at its heels.

There were many posters and presentations on Visudyne at this meeting, both company-sponsored and investigator-sponsored. A speaker, talking about the role of Visudyne in AMD, commented, "The good news is that at least we can help some patients. The bad news is that it's not perfect…In an article to come out in a month, we looked at cases assigned to verteporfrin based on lesion size and change in visual acuity…and the larger the lesion, the greater the loss of vision from baseline…but that was true in controls as well…but always there was less vision loss with Visudyne…So maybe in 2003, even for small, minimally classic lesions, we might consider Visudyne."

Among the Visudyne trials underway that merit watching are:

- VER, looking at shorter treatment intervals. This two-arm trial of 320 patients is looking at treatment at 6 weeks, 3 months and 4.5 months vs. control at only three months. The results will be at ARVO 2004.
- VIO trial, a Phase III study looking at Visudyne in occult-only CNV.
- Adjunctive therapy trials, looking at combining PDT with NSAIDs, Cox-2s, steroids, etc.

TRANSTHERMAL THERMOTHERAPY (TTT) – Interest still there but waning.

Most sources are still doing TTT, and they continue to believe it has a role, although the enthusiasm has been tempered somewhat. One said, "I'm doing TTT for minimally classic CNV only; 100% of occults now get PDT." The Phase III TTT4CNF trial that should answer some of the questions about this therapy is fully enrolled, with data is expected later this year.

Other agents in development for ARMD:

- **ROCHE'S Accutane**. A Phase I trial is underway testing oral administration of Accutane for AMD.

- **Combrestatin analog NV-5-40.** This was found not to be effective in rats. This is a product developed by Tulane University which is considering adjusting the dose in more rats and rabbits to see if that makes it work before giving up.

- **EYETECH'S EYE001**, which is in Phase III. This anti-VEGF is given by intravitreal injection, administered once every six weeks.

- **Statins.** The current thinking is that statins may help in AMD because they are anti-inflammatory, and one researcher suggested that the more lipophilic statins may work best. An Australian researcher has started a two-year, pilot, randomized trial comparing 40 mg simvastatin to placebo in patients at high risk of developing AMD (early AMD before patients qualify for Visudyne). The primary endpoint is progression rate. Another researcher found that statins and aspirin may have efficacy in preventing CNV in AMD patients. Compared to dry AMD controls, CNV patients were:
  - ~60% less likely to have taken statins.
  - ~60% less likely to have taken aspirin.
  - More than twice as likely to be current smokers.

- **WYETH'S rapamycin**. Investigators reportedly plan a primate study of oral rapamycin to treat AMD. A poster also reported that CNV development was inhibited by both oral (2.5 mg/kg/day) and subretinal administration in a gel.

DIABETIC MACULAR EDEMA AND UVEITIS

BAUSCH & LOMB AND CONTROLLED DELIVERY SYSTEM'S Retisert (formerly Envision) – Hopes are fading.

DME Trial. Retisert is a back-of-the eye implant that delivers the steroid fluocinolone acetonide for up to three years. Results of a pivotal multi-center trial of 80 patients showed efficacy but excessive side effects, and development will be delayed. In this trial, 0.5 mg and 2 mg Retisert were compared to standard of care (macular grid laser or observation). During the trial, the 2 mg dose was discontinued, so final results are available only for the 0.5 mg dose.

B&L officials said there will be a up to a three year delay in filing Retisert for the DME indication. The FDA apparently has requested information on additional implants before it will accept the application. B&L and Controlled Delivery Systems said they will assess the impact of the requirement for additional data when the analysis of the 12-month data from the second Phase III DME trial, which comprises approximately 190 patients, is available. That data analysis is expected to be completed by the end of 2003.

12-Month Results of Retisert DME Trial

Measurement	0.5 mg	Standard of Care	p=value
Primary Endpoint: Reduction in macular edema/retinal thickening to zero	48%	25.0%	p<.05
Secondary Endpoint: Improvement of visual acuity of ≥15 letters	19.5%	7.1%	Nss
Secondary Endpoint: Decrease of visual acuity of ≥15 letters	4.9%	14.3%	Nss
Improved for stable vision	>70%	50%	p=.08
Worsening of diabetic retinopathy score	5.15%	29.6%	N/A
Adverse Events			
Overall incidence	58.5%	10.7%	N/A
Serious increase in IOP	19.5%	0	N/A
Cataract progression	54.87%	0	N/A

Severe Uveitis.
A small substudy of the Retisert posterior uveitis study looked at eight eyes in seven patients. Average IOP increased from 11.8 pre-implant to 16.6 over time. A researcher said he would still use Retisert for severe uveitis, despite his findings and despite the DME side effect data "because there are not a lot of alternatives." Another doctor said, "Even if Retisert has a 12% glaucoma rate, this may be worth using in worst-case uveitis."

B&L and Controlled Delivery both indicated that there has been no change in their development program for the use of the Retisert implant for the posterior uveitis indication.

New Dosing Regimen. A study of a 0.1 µg/day dose and a 0.5 µg/day dose was compared to control in 46 rabbits. The researcher concluded that the 0.5 µg/day release rate significantly inhibited inflammation, "We feel this supports the rationale for the ongoing clinical trial of the 0.5 device. The 0.1 µg/day release rate is not available for humans but may be available in the future."

The moderator asked, "It seems clear that more steroid is better, so how does this compare to triamcinolone in potency?" The presenter responded, "It is slightly more potent than triamcinolone, about 1.2 times more potent."

GLAUCOMA

PFIZER'S Xalatan (latanoprost) – The marketing wars continue.

Pfizer was giving a big push to Xalatan as a first-line treatment for glaucoma. Pfizer was emphasizing its head-to-head study comparing Xalatan (latanoprost), Allergan's Lumigan (bimatoprost), and Alcon's Travatan (travoprost). This 12-week, masked evaluator, randomized, multi-center trial found: All there were of equal potency in lowering IOP, but there was the least hyperemia with Xalatan. There was no difference in IOP lowering at 8 am.

One marketing issue that has helped Travatan so far has been the number of drops there are in each bottle. Some doctors had insisted Travatan lasts longer than Lumigan or Xalatan, but an optometric educator said he did his own test and found that Lumigan goes further. At ARVO, an independent Spanish study concluded the most drops are in the Travatan bottles: Xalatan 27 drops, Xalcom 28.33, Lumigan 25.09 and Travatan 28.86.

XLT Trial Results

Measurement	Xalatan	Lumigan	Travatan	p-value
IOP at 8 am at Week 12	-8.6	-8.7	-8.0	---
Adverse events	64.0%	75.9%	68.8%	---
Systemic adverse events	16.9%	18.2%	16.7%	p=.015
Medication-related adverse events	51.5%	68.6%	58.7%	p=.003
Hyperemia	47.1%	68.6%	58.0%	---
Eye irritation	6.6%	10.9%	4.3%	---

BAUSCH & LOMB'S FISER B105

B&L is working on a new form of timolol 0.5%. By using a mucoadhesive vehicle of sodium hyaluronate, the company hopes to allow QD delivery instead of the usual BID delivery and to make it more tolerable. Early data is promising.

Measurement	Fiser	Timoptal	p-value
Burning	20%	70%	p<.05
Tearing	25%	35%	Nss
Dryness	15%	60%	p<.05
Itching	10%	55%	p<.05
Soreness, tiredness	25%	35%	Nss
Blurry/Dim vision	20%	25%	Nss
Foreign body sensation	15%	65%	p<.05

DRY EYES

Approximately 60 million people world-wide use artificial tears for dry eye (keratoconjunctivitis sicca, KCS). An Allergan report estimated that more than four million people in the U.S. see an eye care professional for dry eye symptoms annually, and up to 1.5 million of these have moderate to severe symptoms.

ALCON'S 15(S)-HETE – Interesting but very early.

Alcon is working on its own dry eye treatment, 15(S)-HETE, a mucin secretagogue, to compete with Allergan's Restasis and Inspire's INS-365. Rabbit data was presented at ARVO indicating that 15(S)-HETE protects the corneal epithelial cells and restores tear film integrity. A Phase II trial is just starting, with dosing BID and four times a day. Although 15(S)-HETE is aimed at all dry eye, only patients with moderate or worse dry eye are included in the Phase II trial.

ALLERGAN'S RESTASIS (Cyclosporine) – A good start out of the gate.

A Wisconsin study found the incidence of dry eye is 13% over five years in people age 48-91. People taking diuretics and/or antihistamines were at increased risk of developing dry eye, while people taking ACE inhibitors were at decreased risk. Most ophthalmologists questioned at the meeting have not started using Restasis yet, but all said they plan to do so soon. For instance, a Maryland doctor said he was impressed with Restasis and plans to give it to all of his patients, first line. So far insurance has covered it in every case, he said, but he noted that not all pharmacies have it yet. He has not yet used it for blepharitis or post-menopausal women, but he plans to start.

Cyclosporine eye drops can be compounded in a lab, but a speaker urged doctors to buy the commercial product, Restasis, saying it is more consistent. An Arizona ophthalmologist cited problems with stability and consistency of compounded cyclosporine, pointing out that Restasis is a unique emulsion technology – an oil-based ophthalmic emulsion that is designed to solubilize cyclosporine. The same vehicle (emulsion) is the basis for Allergan's over-the-counter Refresh Endura artificial tears.

A speaker outlined who he sees as candidates for Restasis -- people who:

- Use artificial tears more than four times a day.
- Have frequent, chronic symptoms.
- Have functional lacrimal glands.

The cost of Restasis is $80-$120 a month – if patients are able to get two treatments out of a vial. Patients are supposed to put one drop in each eye every 12 hours. Speakers

recommended patients be advised to start the medication at night, then put the vial in the refrigerator overnight and put in another drop from the same vial in the morning. A speaker said, "This is not p.r.n. like artificial tears. This is b.i.d…Using one vial this way for two doses, cuts the cost."

Patients can and perhaps should keep using artificial tears when they first start Restasis, which takes some time to really take effect. However, they should use non-preserved artificial tears (e.g., Allergan's Refresh) because "any added emulsion may be poorly tolerated" with Restasis. Gel emollients are not recommended with Restasis. A speaker said, "Patients notice symptom reduction in one month…Key signs continue to improve for three months…and significant improvement in signs and symptoms is seen by six months." Ocular burning occurs in 17% of patients.

Speakers answered some common questions about Restasis:

- *If Restasis is not enough, should artificial tears be added or the dose of Restasis increased?* "Patients can use preservative-free artificial tears between doses of Restasis...Patients already on artificial tears should not stop right away when they start Restasis…the dose of Restasis should not be increased above twice-a-day."
- *Why does Restasis take so long to work?* An Allergan official said, "It doesn't take six months. You see an effect right away, but the effect increases over the first six months." A doctor added, "You need to tell patients to be patient."
- *Can Restasis be used in children?* A doctor said, "Because of the low systemic levels, I see no reason not to use it in pediatrics. I would consider that in my practice without hesitation."
- *Are there issues with irritation?* "Yes. There is a 17% incidence of ocular burning. It can sting. If you are telling them to refrigerate before the second drop, prepare them for a sting. Say, 'That is the therapeutic effect. As the eye becomes more healthy, you might feel it a little more.'"
- *How long should it be used?* "This is a life-long maintenance medication."

Among the other conditions for which ophthalmologists said they are using Restasis include:

- Blepharitis
- Blepharoconjuctivitis
- Staphylococcal hypersensitivity
- Herpes
- Keratoconus
- Post-LASIK

Progress is being made with reimbursement for Restasis, company officials and other sources agreed. An ophthalmologist said, "So far, Restasis is only on a few plans…That will come with time." Another doctor said, "The vast majority of my patients have been handled by co-pays on insurance plans. The military covers it, too."

Not every pharmacy has Restasis yet. One doctor said, "Walgreen's has been very helpful, but Wal-mart has been a pain in the neck."

INSPIRE PHARMACEUTICALS –Mixed results.

- **INS-365 (diquafosol).** There were mixed results from the 24-week, pivotal, Phase III trial of INS-365. There were two co-primary endpoints in this trial, and the drug met the objective one (corneal staining) but failed to meet the subjective one (symptoms).

1. **Corneal staining at 6 weeks: met.**
   a. 1% and 2%: At weeks 2, 4, 6, 8, 10, 12 and 24 there was a statistically significant ($p<.05$) reduction in cornel staining compared to placebo.
   b. There was no statistically significant difference between 1% and 2%, but 1% trended to have a slightly greater effect.
   c. A significant treatment effect was observed as early as 2 weeks after initiation of treatment.
   d. Corneal staining reversed direction one week after discontinuation of active treatment.

2. **Symptom relief at 6 weeks: not met** (by intent-to-treat analysis). In the protocol analysis, patients in the 2% group cleared their symptoms at a higher rate than placebo (21% vs. 15%, but the difference was not statistically significant ($p=0.193$).

   If both eyes of all dry eye patients were included in the analysis, an official said this endpoint would have been met. According to the poster: "An analysis of all dry eyes that accounted for the correlation between eyes showed significant differences in favor of 2% diquafosol vs. placebo at Weeks 8 and 10 ($p=.0014$ and $.0019$, respectively) as well as at the primary Week 6 endpoint ($p=.048$), and differences approached significant at the Week 12 endpoint ($p=.0065$)."

   At the primary time point of six weeks, mean Schirmer test scores were significantly higher in the 1% drug group vs. placebo but there was no statistically significant difference from placebo in the 2% group.

An official said approval is being sought for the 2% formulation because (1) symptoms were better with the 2% formulation and (2) there was no statistically significant difference between the 1% and 2% formulations. The expected label is: "For reduction of corneal staining associated with dry eye." INS-365, which will be administered four times a day, will be sold in a four-dose bottle that can be opened, re-sealed and re-opened for a 24-

hour period, after which point it must be discarded. Allergan has the responsibility for developing any longer-acting version.

Company officials said the NDA will be filed by mid-year, and they believe the data they will be submitting is sufficient for FDA approval. The application will be based on this Phase III trial along with a previously completed Phase II trial. An official explained, "At an October 2002 meeting with the FDA on endpoints, the FDA accepted surrogate endpoints, and that's what our application is based on."

Other trial data also will be given to the FDA in support of the application, including:

(1) **Study 104.** This was a prior Phase III trial that failed. It showed safety but did not show efficacy in reducing symptoms. An official said, "The FDA doesn't allow adjusting for baseline, but if you adjusted for baseline in this trial, we would meet the endpoint."

(2) **CHAMBER study.** This trial is completed, and data cleanup is underway. Results will be released by press releases before the end of June 2003. Patients were put in a dry environment (a chamber), and their eyes dried out, which an official described as "great for symptom measurement." He declined to identify the primary endpoint, saying, "It is related to symptoms and overall ocular discomfort, but we are negotiating a final analysis endpoint with the FDA now, and we want to complete that before we unmask the data."

Asked how INS-365 would compete with Restasis, an Inspire official said, "Restasis use is based on inflammatory dry eye. Our Sjogren's patients did as well as non-Sjogren's patients, so we expect a broader label. And INS-365 is faster-acting (1-2 weeks)."

Results of Study 105 of INS-365 at Week 6

Measurement	Placebo	1.0% INS-365	2.0% INS-365
Number of patients	176	176	175
Symptom clearance by protocol analysis	15%	N/A	21% (p=.193)
Reduction in Schirmer score	~2.4 mm	~4.2 mm	~3.5 mm
Ocular adverse events	27%	22%	30%
Withdrawal due to adverse events	7 patients	1 patient	3 patients
Burning/stinging	2%	3%	7%

Testosterone Cream

A poster reported on the use of testosterone cream, applied to the eyelids, as a treatment for dry eye. More than 50% of 28 patients reported a significant decrease in dry eye symptoms. It was least effective in males, and most effective in post-menopausal women. It is not recommend for children or patients with: prostate cancer, elevated PSA, cardiovascular disease, liver or kidney disease.

Contact Lenses

An interesting study from the U.K. looked at the protozoan *Acanthamoeba*, which can contaminate contact lens storage cases, attaches more frequently to one brand of contact lens than another. A previous study found that surface treatment of Bausch & Lomb's PureVision lens was not responsible for the high level of amoebal attachment found in that study. In this study, researchers compared Bausch & Lomb PureVision lenses, Novartis/Ciba Vision's Focus Night & Day lenses, and Johnson & Johnson/Vistakon's Acuvue lenses. Researchers found that significantly more *Acanthamoeba* attached to Focus Night & Day and PureVision silicone hydrogel lenses than to the conventional Acuvue hydrogel lenses. Commercial surface treatment of the Focus lenses actually increased the attachment of *Acanthamoeba*,.

Intraocular Lenses

Several companies have IOLs in development for cataract patients. Among these are:

- **ACRI.TEC'S AR-1 PC.** This is in preclinical development in Germany. It can be adjusted after implantation, though that requires a second surgical intervention. A researcher speculated that it will be especially good in children.

- **ALCON'S AcrySof.** The newest generation is the SA60AT, which follows the MA60BM. A study compared these two lenses and reported the surprising finding that the newer SA60AT has a higher incidence of anterior capsule contraction syndrome (ACCS) than the older MA60BM. The researcher speculated that this may be due to the difference in the haptic design and/or the material.

Measurement	AcrySof SA60AT	AcrySof MA60BM	p-value
Number of patients	230	188	---
Mean follow-up	3.24 months	6.42 months	---
ACCS	2.6%	0	p=.03

Refractive Surgery

Refractive surgeons questioned at the meeting do ***not*** believe there is an upturn nationally in refractive procedures. Sources at Bausch & Lomb, Allergan and other companies all agreed

with this outlook; they said they are not hearing any increase in procedures from the doctors they see. On average sources predicted that 2003 will be relatively flat compared to 2002. They insisted that refractive procedure volume is tied to the economic situation, and they predicted refractive procedures will not increase significantly until the economy improves. A New York doctor said, "If the Canadian experience is any predictor, there will be a low rise that will be driven by custom ablation…Last summer was flat, so this summer will be a really good indictor." A Texas doctor said, "Our volume is up, but we are the only center in town that is up…Volume is on the way back up in our practice, but slowly. We are not at the level we were prior to September 11th, but we've seen an upward blip…But any significant increase will be associated with an economic pickup." An Ohio doctor said, "Our volume has increased because we are the only center in the area that offers custom ablation."

Centers offering custom ablation said they had seen an uptick in procedure volume, and they attributed it to the custom ablation, but they did not believe this heralded a national pickup in procedures. Most of these sites were either the only site or one of just a few centers offering custom ablation in their area. A New York doctor said, "Custom cornea really is bringing in patients. The 'technical' segment of the market (techies) is very interested in this…When Visx and B&L get approval for their custom cornea systems, it will really take off." An Arizona doctor said, "Some patients are waiting for custom cornea. There definitely is demand, and people will pay extra for it." A Texas doctor said, "Wavefront is driving an increase in our business. Patients are willing to pay more for it, and they normally choose it." A Georgia doctor said, "Custom cornea has had no impact, and it won't." A Florida doctor said, "Custom cornea is not increasing refractive volume, and I don't expect it to." An Ohio doctor said, "We do custom ablation on all patients who qualify for it, but we don't charge extra for it…Custom ablation has brought in the patients who were on the fence."

MISCELLANEOUS

JOHNSON & JOHNSON'S Remicade

Researchers are encouraging Johnson & Johnson to do a trial of Remicade (infliximab) for ulcerative keratitis, and data was presented on the use of Remicade in uveitis. A trial of 12 patients tested 3-5 mg/kg administered on weeks 0, 2, and 6. Assessments were made at weeks 10 and 50. At 10 weeks, vision improved in five patients, worsened in one and was stable in six. The frequency of flares decreased in six patients. Only four patients have completed 50 weeks of treatment so far, but all were graded a success at both the 10 week and 50 week points. Two patients with pre-standing uveitis NV experienced vitreous hemorrhages; one patient developed migratory arthritis, which was not thought related to the drug; and one patient and symmetric polyarthritis.

Researchers concluded that infliximab:

- May be an effective immunosuppressant short term with success in 11 of 12 patients.
- Is effective and well-tolerated for longer treatment in four patients who reached one year.
- Works quickly. By 10 weeks, all the patients had clinically definable improvement, and one patient got better within days/week of treatment, though vision faded over time.

SURMODICS – Entering A New Area : Ophthalmology.

SurModics is collaborating on a novel drug delivery device to compete with B&L's Envision/Retisert. It reportedly is easier to implant than Envision, lasts about six months, and can be removed. An official said it has not been decided which eye condition will be targeted initially.

This AMD treatment device actually was developed by Doheny Eye Institute at the University of Southern California, using SurModics polymer coating technology. It is a helical intravitreal implant, shaped like a corkscrew, that elute triamcinolone (Kenalog). So far the device has been made out of stainless steel with a uniform polymer coating (not bio-erodable) that is 25-59 µm thick, but future designs probably will be a non-ferrous alloy. A researcher said, "We also looked at several other drugs, and the coating is compatible with a wide range of drugs -- and everything we've tried has worked with this coating."

The doctor overseeing this project at Doheny invented the retinal tack, which is well tolerated in the eye. A researcher from his lab said, "Ultimately we may want something more posterior since steroids are cleared anteriorally."

Doheny/SurModics Drug-Eluting Screw

Design Feature	Advantage
Rigid body of metal	Ease of implantation
Small wire (<25 gauge)	Implantation through "needle stick"
Minimal overall diameter	Pars plana implantation
Low profile scleral cap	Further anchors to eye wall and is covered by conjunctiva
Polymer coating from SurModics containing Kenalog	Controlled elution rate (duration 6-12 months)

To implant the device, the sclera is pierced, then the device "screwed" in. It's a four-step surgical procedure: (1) Initial 0.5 mm transconjunctival needle stick, (2) insertion with

clockwise handle rotation, (3) handle release, and (4) conjunctival covering of the cap.

The elution rate can be adjusted by changing the geometry (surface area) of the device – by increasing the diameter of the wire, by packing the coils tighter, and/or by lengthening the device. At a release rate of <5 µg/day, a researcher estimated that the device would continue to elute for six months or longer, and with design changes and an elution rate of 2.5 µg/day, it might last as long as 2.5 years. A researcher said, "We are getting from 6 mcg to 1 mg on these devices."

In the first animals, it took 5-10 minutes to implant the device, which has an overall dimension of 2.0 x 5.0 mm and releases triamcinolone at 2.5 µg/day for 285 days. More animal studies are planned before the device is taken into human clinical trials.

THE FUTURE OF ANGIOGENESIS

Dr. Judah Folkman gave the keynote address and discussed angiogenesis inhibitors, noting that there are 20 in clinical trials in the U.S. and 50 in trials world-wide. Among the agents he highlighted were:

- Lilly's LY33531.
- Alcon's anecortave.
- Celgene's Revimid.
- EntreMed's 2-methoxyestradiol. He said, "This is very similar to Taxol (Bristol-Myers Squibb, paclitaxel) without the toxicity. EntreMed has done a beautiful job. There is no toxicity of any kind. The problem is the patients just stay on it. There are 1,000 pts in Boston on the waiting list, so there are always shortages…It is self-injected at home…Unless you see the patients you can't understand what the drug does."
- Vitamin D binding protein-macrophage activating factor (DBP-MAF)
- Interferon-alpha. Massachusetts General hospital has stopped radiation therapy for patients with Giant Cell lesion of the jaws; they are using Interferon-alpha for these patients instead.
- Pfizer's SU5416. Dr. Folkman said, "There is extensive and durable recovery of visual function with this agent, and it is maintained."
- AstraZeneca's Iressa.
- Genentech's Avastin. He said, "There was great success in advanced kidney cancer, but it also works for macular degeneration."
- Pfizer's SU11248. When patients become resistant to Gleevec (Novartis, imatinib), oncologists at Dana Farber Cancer Institute are using this, and Dr. Folkman said they are seeing regression in seven days.
- Angiostatin.
- Pfizer's Celebrex (celecoxib). This was found to be an angiogenesis inhibitor after it was FDA approved for other indication.
- GlaxoSmithKline's Avandia (rosiglitazone), which he described as "a powerful angiogenesis inhibitor."
- Novartis's Zometa (zoledronate), a bisphosphenate.
- Genentech's Herceptin (trastuzumab. Dr. Folkman warned: "If a patient is resistant to Herceptin, don't stop the drug, just add another anti-angiogenesis agent."

Dr. Folkman's take-home message was: "Angiogenesis is providing a unifying principle for diseases which, although they have different names and are treated by different specialists, are dominated by the same pathologic process and can be treated with the same class of drugs. So, the ophthalmologist trying to stop angiogenesis in the eye is treating the same process as the rheumatologist in the joint, the gynecologist in endometriosis and the urologist in BPH and prostate, renal, and bladder cancer."