Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Retinal specialists are expecting to use the new AMD therapies in combination, but there is no consensus on which are the best combinations. ♦ Concern over the pooled data and carcinogenicity of Eyetech's Macugen for AMD appears to be lessening. ♦ In glaucoma, the same marketing wars that have raged over Travatan-Xalatan-Lumigan are likely to occur when combination products (prostaglandin+beta blocker) are approved. ♦ LASIK procedure volume has picked up, but the 2004 outlook is still extremely dependent on the economy. Use of custom ablation is continuing to increase. ♦ Refractec's CK appears to be catching on. ♦ Products to watch: (1) Neuroprotectives, particularly Allergan's memantine and Posurdex and Teva's Copaxone; (2) Allergan's preservative-free formulation of triamcinolone; (3) Alcon's ReSTOR accommodating IOL and AMO's ReZoom lens; (4) Novartis' pimecrolimus drops for dry eye; and (5) rheophoresis.

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY (ARVO)

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Research presented at ARVO shed new light on a variety of topics, including:

AGE-RELATED MACULAR DEGENERATION (AMD)

Right now, retina surgeons have only three options for treating AMD – Visudyne (PDT), triamcinolone acetate (Bristol-Myers Squibb's Kenalog), or TTT (transpupillary thermotherapy), but soon there may be several other drugs. Asked how these new agents will change the way they treat patients, doctors offered a variety of combination scenarios, including:

- Macugen + PDT. A U.K. doctor commented, "I wouldn't stop PDT with Macugen; the benefit is not great enough with Macugen to do that."
- Macugen + anecortave ± PDT. One doctor suggested, "We could give an anecortave, then Macugen every six weeks for six months, and then another injection of anecortave – and maybe we wouldn't have to give anything more." A Macugen researcher said, "We may and will see combination therapy, but I would encourage doctors to put patients in trials rather than play in the kitchen." Another researcher said, "Combination therapy is the future. No one drug will knock it all out. We probably can't keep giving intravitreal injections indefinitely. The idea of combination therapy is like treatment for HIV or cancer."
- Anecortave + PDT.
- Lucentis + anecortave ± PDT.
- Lucentis + PDT.

Sources generally agreed that it probably won't be feasible to combine Macugen and Lucentis since both are anti-VEGF therapies. A U.K. doctor also pointed out that there could be a volume issue in combining Macugen with either Lucentis or triamcinolone.

How will reimbursement affect these choices? Most doctors simply are not worrying about that, assuming that CMS will pay for anything that works. A few sources took a more conservative approach, predicting that CMS would make them choose one therapy or another until and unless trials are conducted to prove an added benefit to combination therapy.

ALCON'S Anecortave

No new clinical data on anecortave was presented at ARVO, but there was a poster on a mouse study on the mechanism of action of anecortave. A researcher said the purpose of the study was to create a baseline model for development of second generation agents and alternative delivery systems. An expert said, "Juxtascleral administration has an advantage over intravitreal – but if one of the new agents shows superior efficacy, that is what will be used.

BAUSCH & LOMB'S Retisert (formerly Envision)

Two-year data were presented on this back-of-the-eye implant that delivers the steroid fluocinolone acetonide for up to three years. The trial began as a comparison of 0.5 mg fluocinolone, 2 mg fluocinolone, and standard of care. The 2 mg dose was discontinued. Patients will be followed for an additional two years. Another Retisert trial completed enrollment 1.5 years ago, and that data should be forthcoming.

24-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	46.2%	14.8%	N/A
Mean change in visual acuity	+9.3	-1.9	p=.03
Serious Adverse Events			
Overall incidence	31.7%	0	N/A
Cataract progression	13.3%	77.4%	N/A

EYETECH PHARMACEUTICALS/PFIZER'S Macugen (pegaptanib sodium)

At least twice, Macugen researchers presented the same pooled analysis of Macugen VISION trials that was previously presented. A researcher also offered new safety data from those trials. As a reminder, this is an analysis of 1,190 patients from 117 centers, with 7,545 injections. There were 12 cases of endophthalmitis, but the researcher said the injection protocol was changed, and for the last 10 months there has not been a case of endophthalmitis. An investigator said, "Macugen has shown proof of principle, and it appears to be promising…It is not a cure, and it is not something that will make people jump up and down and say, 'Eureka! I've had a

Pooled Analysis of Macugen VISION Trials

Measurement	Macugen 0.3 mg	Macugen 1.0 mg	Macugen 3.0 mg	Sham (standard of care)
Primary endpoint: % patients losing <15 letters (3 lines) of vision	70% p=.001 206:294	71% p=.003 213:300	65% p=.0310 193:296	55% 164:26
At 6 weeks	-1			-4.0
At 12 weeks	-3.2			-6.3
At 54 weeks	-8.0			-15.0
Reduction in severe vision loss (≥6 lines of vision loss)	10%			22%
Safety				
Most common ocular events	34%			28%
Punctate keratitis	32%			27%
Severe inflammation	0			0
Moderate inflammation	1%			0
Mild inflammation	13%			5%
Endophthalmitis	1.3% per patient/year			0.1% per patient/year

Pooled Safety Analysis of VISION Trials

Measurement	Macugen patients n=892	Sham (standard of care) n=298
Completed study	90%	92%
Mean number of treatments	8.5	8.6
Severe vision loss	10% (p<.0001)	22%
Vascular hypertensive disorder	10%	8%
Proteinurea	3%	3%
Serious hemorrhagic adverse events	1%	1%
Peripheral embolism and thrombosis	0	0
Pulmonary embolus	0	0
Coronary artery disorders	0	1%
Stroke	1%	0
TIA	1%	1%
Deaths	2%	2%
Eye pain	34% majority mild	28%
Severe inflammation	0	0
Mild inflammation	13%	5%
Endophthalmitis	12 cases, 1.3% per patient year	---
Traumatic cataract	5 patients, 0.6% event rate	---
Retinal detachment	5 patients, 0.6% per patient/year	---

change in vision a day after an injection'…but it should make the person see better than a twin (who didn't get Macugen) at a year."

An Eyetech official responded to two concerns that have arisen with Macugen:

1. Carcinogenicity. Eyetech corporate documents recently revealed:
"…in a test of Macugen and its metabolites in the Syrian Hamster Embryo Assay, which we performed at the request of the FDA, the results were negative for carcinogenic potential. However, one of the animal tests that we performed suggests that two of the metabolites of Macugen are compounds as to which there may be carcinogenicity risk. As a result, we may be required to conduct additional carcinogenicity testing of Macugen. Based on our discussions with the FDA to date, if we are required to conduct further carcinogenicity testing of Macugen in connection with its use in the treatment of wet AMD, we believe that the FDA will allow us to conduct any such testing as a post-NDA approval study…"

The Eyetech official said that none of the animal studies with Macugen – from hamsters to primates – have shown any carcinogenicity issues. However, he said one of five strains of bacteria showed a small increase in revertants when an E. coli Ames test was run. He said, "Then, the FDA requested a SHE assay, and that was negative."

Asked about the FDA's request for any further carcinogenicity studies, the Eyetech official replied, "All indications are that we don't have to do a standard (two-year) carcinogenicity study, but we don't get that waiver until we actually file the NDA, which will be in 3Q04. If we don't get a waiver, then I understand the study would be post-approval." Another expert said he believes the company has a good chance of getting the waiver or being allowed to do trial as a post-marketing study, "AMES is notorious for artifacts, and if the SHE study was negative, I might be comfortable with this as a post-marketing study." However, all other sources were uniformly dubious that the FDA will allow Macugen to do a carcinogenicity tox study post-marketing.

2. Pooled data. The two pivotal trials, VISION, have only been presented as pooled data. Eyetech has said both are statistically significant on their own, but has refused to release details on the individual trials. This raised some eyebrows. One expert said, "I find the data confusing in the way it is presented." There also was this exchange between a moderator and an investigator:

> **Moderator**: "Will we ever see the findings reported for the Macugen+PDT subgroup vs. the Macugen naïve group vs. Sham without PDT?…I think that is something we need to see."
>
> **Speaker:** "When it is written, the analysis will be more detailed, but the numbers are too small to make a significant comment."

However, an investigator said the results are statistically significant for each subtype in the individual studies, adding that the numbers are small. He commented, "In all three subtypes, there was a statistically significant benefit, but the numbers are small."

A doctor in the audience wanted to know if any of the beneficial effects from Macugen could be due simply to the intravitreal injection alone. A researcher responded, "We agonized about that…and we can't rule that out completely… but I doubt it...Most of us felt uncomfortable keeping patients on intravitreal injections when we didn't know the side effects."

An Eyetech official said the pooled presentation is similar to how QLT Therapeutics presented its pivotal TAP trial data, "TAP was two trials, and they were presented as pooled data. We are doing the same thing." However, a TAP investigator said the two sets of trials (TAP and VISION) are different, "With TAP we released the results of the primary endpoint in both trials, not just the p-value, and we formally stated that the other measurements were identical in the two groups, so it would have just overwhelmed everyone with data to list them separately. All the outcomes were so similar that it made sense to pool them. But the FDA did separate analyses for the advisory panel, and we published all the data in great detail."

Other news about Macugen includes:

- Eyetech is working on an extended release formulation of Macugen.
- The AMD subset analysis is still ongoing.
- A source said Eyetech was hoping to get experts to write a "white paper" on preventing infection with intravitreal injections, but the data were not there to support that. Instead, experts offered to do a consensus statement. The status of this is uncertain.
- Efficacy results of a 169-patient, 12-week, Phase II trial in DME was released shortly after ARVO. The safety data was still being analyzed. The trial compared Macugen at 0.3 mg, 1 mg, and 3 mg administered every six weeks to sham. Investigators found the optimal dosing to be 0.3 mg, the same dose being used in the pivotal AMD trials.

Macugen Phase II DME Study

Vision Change	Macugen 0.3 mg	Sham	p-value
Vision gain ≥0 lines	73%	51%	.02
Vision gain ≥2 lines	34%	10%	.003
Vision gain ≥3 lines	18%	7%	N/A
Reduction in retinal thickness	50.79 micrometers	12.68 micrometers	N/A

GENAERA'S squalamine lactate (MSI-1256F)

Data were presented from a 40-patient, four-month, Phase I/II trial of intravenous administration of squalamine in wet AMD. The study tested two doses – 25 mg/m^2 and 50 mg/m^2, infused initially for 90 or 180 minutes, and later to 45 minutes, at Weeks 1, 2, and 4. The company hopes to get infusion times down to 20 minutes in the future.

Researchers reported some mild injection site pain, phlebitis, and injection site inflammation. No severe adverse events were deemed related to the study drug. There also were no elevated liver enzymes, no apparent effect on IOP, and no apparent adverse cardiac events. A researcher commented, "There are only 200 individuals world-wide who have been exposed to this drug…So, we are just scratching the surface of possible adverse events. I don't doubt we will see something…but we have taken a very optimistic and very encouraging first tiny step in investigating this drug…In our study, we saw no severe adverse events."

Measurement	2 weeks	4 weeks	2 months	4 months
Positive gain of ≥3 lines	25%	33%	33%	26%
Stable vision	72%	67%	64%	74%

A Phase II safety trial in 18 patients, testing three doses is beginning. Genaera said it intends to conduct three Phase II trials and begin Phase III trials in early 2005.

GENENTECH'S Lucentis (rhuFAB VEGF)

Retina specialists are very impressed with this agent. One investigator raved, "Lucentis will be unbelievable. Patients are doing wonderfully…I think it is magic, and it will change how we treat patients. Combination therapy is not necessary because Lucentis works so well alone."

One question that did come up about Lucentis is when to stop therapy. An expert noted that untreated AMD patients generally form scars at one year and most PDT patients scar by two years. He suspected that Lucentis won't scar even at two years, so it would need to be continued until the patient does scar. He said, "Ten years of treatment with Lucentis would not be good for the eye or for patient perception of treatment, but possibly we could use one or two PDT treatments to help the patient scar over after Lucentis." A Genentech researcher said, "There is absolutely no answer at this stage…We will be analyzing Phase II and Phase III data to see if we can spread out dosing, to see if we can stop after a certain number of injections and then treat recurrences when they occur…And people also are looking for a better means of administration than intravitreal."

Ongoing Lucentis trials include:

- **FOCUS**: PDT+Lucentis vs. PDT+sham. This two-year trial completed full enrollment in January 2004.
- **MARINA**: Sham vs. 300 µg Lucentis vs. 500 µg Lucentis. This is a Phase III trial in minimally classic/occult AMD.
- **ANCHOR**: Sham vs. 300 µg Lucentis vs. 500 µg Lucentis. This trial in predominantly classic AMD is about two-thirds enrolled.

GENVEC'S adPEDF

A researcher presented interim results on 20 of 24 patients enrolled in a Phase I study of this gene therapy treatment for AMD. Administration was by a single ($10^{6.0}$ pu) intravitreal dose in patients with severe disease, with a goal of determining dose-limiting toxicity. The therapy was well tolerated at all doses, with no DLT, no endophthalmitis, and no drug-related severe adverse events. A researcher said:

- "There were some patients with mild inflammation, and some patients with an increase in IOP, possibly related to inflammation, all of whom responded to optical medications."
- "The majority of patients did not have induction of neutralizing antibodies."
- "Are the pressure changes due to the natural history of the disease or to the adPEDF? It is hard to tell without a control group."
- "The protocol precludes conclusions relating to efficacy...but many patients did show improvement in vision…and there was evidence of improvement of the visualization of the retina over time...Whether this is chance or activity is a matter of speculation."

An adPEDF researcher said, "It may not be beneficial to give adPEDF more than three times." Her poster concluded:

- "A single intravitreal injection of adPEDF results in a large increase in PEDF levels in the retina, choroid, and sclera."
- "PEDF expansions gradually decline to low levels that are still significantly higher than baseline at one month post-injection."
- "A second injection one month after the first, results in another increment in PEDF levels. However, the magnitude of the elevations is substantially lower than the first injection."
- "A third injection, performed a month later, results in a small but significant rise in PEDF levels in the choroid and sclera but not significant elevation in the retina."
- "It is difficult to make definitive conclusions regarding the feasibility of repeated intravitreal injections of adPEDF in humans."

MIRAVANT'S SnET2

In 2002, SnET2 failed to meet the primary endpoint in its two-year (103-week), 920-patient, pivotal trials (98-EA001 and 98-EA004), which resulted in Pharmacia pulling out of its marketing agreement. However, Miravant, after consulting

with the FDA, re-analyzed the trial data, and in March 2004 resubmitted SnET2, based on a per-protocol analysis of the lower of the two doses in the pivotal trials (0.5 mg/kg).

Researchers for SnET2, which uses a 664 nm laser by Iridex, presented efficacy and safety data at ARVO. In terms of safety, there were no liver enzyme elevations, no back pain, no severe vision loss in the first seven days. The photosensitivity was reported as dose dependent, predominantly mild and transient, and self-limiting.
At one session the audience reacted cautiously. They had questions about the use of a per-protocol analysis (where the visual acuity results were statistically significant) instead of an intent-to-treat analysis (where the visual acuity results were borderline).

Among the issues facing this potential competitor for Visudyne are:

1. Re-analysis of data. Can a re-analysis of two pivotal trials be used for approval? Since the resubmission was done in consultation with the FDA, it would appear that this is possible.

Pooled SnET2 Pivotal Trial Results

Measurement	Placebo n=183	SnET2 0.5 mg/kg n=372	SnET2 0.75 mg/kg n=372
Incidence and duration of photosensitivity adverse events			
Per patient	2.7%	9.6%	18.8%
Per administration	1.1%	4.8%	11.2%*
Median time to onset	2 days	5 days	5 days
Median duration	5 days	4 days	7.5 days
Severe photosensitivity	None	None	Few
Moderate photosensitivity	Mostly	Some	Some
Mild photosensitivity	Some	Some	Mostly
Symptoms or other surgical/ medical procedures drug-related	16.9%	14.0%	~15.4%
Acute vision loss within 7 days of treatment			
Per patient	0.55%	0.27%	1.1%
Per administration	0.22%	0.11%	0.45%
Back pain			
In patients with adverse events	0.55%	0.54%	1.1%
Per total administrations	0.22%	0.23%	0.45%
Side effects			
Retinal hemorrhage	0.%	3.0%	3.5%
Retinal disorder	3.8%	3.5%	4.8%
Abnormal vision	1.6%	3.2%	2.2%
Macular degeneration	1.6%	2.2%	2.4%
Patients with treatment-related severe side effects (all required hospitalization)	---	1 "moderate" extravasation	2 "severe" extravasations, 1 "severe" allergic reaction
Site adverse events of patients with adverse events	1.6%	5.1%	8.3%
Adverse events per total administrations	0.65%	2.2%	3.9%
Vision system adverse events likely related to drug	7.1%	5.4%	8.6%

* The poster also reported this as 13.1%, but a company official insisted the 11.2% figure was correct.

2. Sun exposure. How long a warning is the label likely to have with respect to sun exposure post-treatment? The company is seeking a seven-day warning, based on solar simulation studies. These were done on doses from 0.3 mg/kg-1.6 mg/kg, using a MED (minimal erythmal dose) standard that measured response to exposure to the equivalent of one hour of noon-day sun in the summer in the contiguous 48-states. An investigator said, "We found that a 0.6 mg/kg dose dropped to a safe level at four days. I don't think the FDA will give us that, and we are applying for seven days, but we could live with slightly longer – say, 10 days." Another investigator said, "The solar simulation and PK studies support one-week precautionary measures." A U.K. doctor said, "Probably there will be a ban on sun for two weeks, but it could be four weeks."

3. Cost. Most retina surgeons who are interested in offering PDT have already invested in a laser and have worked Visudyne into their practice. It could be hard for Miravant to compete with Visudyne – unless it is priced lower. A Miravant official said the company is in discussions with possible marketing partners but insisted it will not be Pfizer. She said, "The laser is a potential obstacle, so our marketing strategy would consider that, and there will be a program to overcome that objection."

Among the advantages an investigator suggested that SnET2 has over Visudyne are:

- **Efficacy** – in all lesions.
- **Labeling** – possibly a need for fewer treatments (maybe only three).
- **Side effects –** no back pain and no liver enzymes elevations.
- **Cost** – potentially lower than Visudyne.

QLT THERAPEUTICS' Visudyne (verteporfrin)

Doctors are divided on what the approval of new AMD agents will mean for Visudyne. A Florida doctor said, "PDT will go away when rhuFAB (Genentech's Lucentis) is approved." A West Coast retina specialist said, "We stop Visudyne after three to four treatments – once the patient forms a scar and subretinal fluid is gone on OCT. But I'm not sure the other agents will reduce our use of Visudyne. I think combination therapy is where we are going in the future, as they do in cancer."

Other AMD Therapies

➢ **Rheophoresis.** Rheophoresis is approved in Canada, and a pivotal MIRA-1 trial is ongoing. Enrollment is expected to be completed in the fall of 2004.

Doctors really aren't sure what to make of this blood

filtration system for AMD. Most sources were a little squeamish about it and concerned about its somewhat tarnished history. While they admit the data appears to indicate it may have some beneficial effect, many are still reluctant to get involved. However, a growing number of doctors are reconsidering their earlier skepticism, and doctors are asking to become trial sites. An older optometrist with AMD in one eye said he has even decided to try it himself. A Florida doctor said, "We decided to participate in the rheophoresis trial. It gives us something to offer patients with no other options. A California surgeon said, "Rheophoresis doesn't seem to be the answer to the public health problem. There are just too many people with AMD to make rheophoresis feasible. If people with AMD changed their diet, exercised, and stopped smoking, they would probably get better anyway without rheophoresis. I think it does work, but it is still probably a short-term answer to a long-term problem because if you stop the treatments, the (large proteins and fatty particles) re-accumulate. And the cost implications to the healthcare system are staggering…I considered participating in a clinical trial of rheophoresis but decided against it."

➢ **TTT (transpupillary thermotherapy).** The key trial of TTT in AMD was fully enrolled with 306 patients in April 2003, so results are likely later this year. A Japanese study suggested that TTT may work by upregulating proteins. An RT-PCR study found that nine genes were upregulated by TTT, including thrombospondin-1, IL-1β, and MCP-1. A French study of TTT in five patients with chronic serous choroidopathy (CSC) showed some remarkable results in patients who had long-term vision loss. Researchers used a lower power (400 nm) laser rather than the usual 810 nm laser.

French TTT Study

Patient #	Visual Acuity	Length of time at that VA	VA 3 months post-TTT
1	20/200	10 years	20/70
2	20/100	8 years	20/40
3	20/70	7 years	20/25
4	20/100	6 years	20/30
5	20/200	4 years	20/70

➢ A Tulane University poster reported on a study indicating the potential benefits of a camptothecin-somatastatin analog conjugate (JF-10-81), noting that it showed no side effects in rabbits at 10^{-5} M and had a suppressive effect on rat CNV when administered intravitreally.

➢ **THERAGENICS** is looking at a low energy (22KuV) radiation treatment for AMD using an extrascleral implanted disc.

DRY EYE

ALLERGAN'S Restasis (cyclosporine ophthalmic emulsion 0.05%) has taken off slower than some had expected, and it is not clear whether Restasis will pick up steam. An Allergan official said both patients and doctors need more education about glaucoma medications and treatments, including Restasis. He said, "Dry eye is a disease of individual responses…You can only decide what works by trying it…People are thinking that Restasis is for more severe patients…I think doctors don't see it as something to use early in the treatment algorithm."

Competitors also are on the horizon that bear watching, including:

➢ **NOVARTIS** has a topical (eye drop) form of its immunosuppressant, pimecrolimus, in development. A Phase II/proof of concept trial is completed, and the company now plans to start a Phase II/III trial in Europe and the U.S. This may be a pivotal trial, but a second, confirmatory study would still be needed, and the company has not firmed up the dosing yet. This is a totally different formulation of pimecrolimus that is used for either Eligard or the oral psoriasis treatment Novartis has in development.

➢ In Mexico, **LABORATORIOS SOPHIA** sells ModusikA Ofteno, its own cyclosporine drops in a proprietary Sophisen carrier. These come in two doses, 0.05% and 0.1%, and a study presented at ARVO indicated that both are comparable in efficacy to Restasis. The company is building a new plant in Mexico that reportedly will be completed in 2006 and will be cGMP compliant. The company would like to bring this product to the U.S. – at a price at least $20 below the $100/month that Restasis costs.

➢ **ALLERGAN** is working on an androgen eye drop. A source said this is in Phase II trials now.

GLAUCOMA

An estimated 2.2 million Americans have glaucoma, and the number is growing. An expert said "There has been steady growth over the past seven or eight years. It has plateaued slightly, but we are still in a growth phase because (a) more patients are being diagnosed, and (b) there are more first-line therapies." Only about half of glaucoma patients in this country have been diagnosed, and even when patients are diagnosed and started on glaucoma medications, many are not compliant or drop therapy altogether.

Allergan-Sponsored Study of Prostaglandin Compliance

Measurement	Pfizer's Xalatan	Alcon's Travatan	Allergan's Lumigan
% of patients on drug at least a year	69%	70%	68%
Total days on therapy	281	287	291

In April 2004, Prevent Blindness America, with support from Allergan, launched Protect Vision, a program to help optometrists and ophthalmologists improve the care and management of glaucoma. The physician-directed program includes advertising in trade publications, an interactive website (www.ProtectVision.org), and a variety of resources to help doctors keep patients on their glaucoma medications and to educate family members and caregivers who come to eye doctors' offices with patients. Dr. George (Jack) Cioffi, a glaucoma specialist with Devers Eye Institute in Portland OR, said, "At least 50% of patients will be missed by screenings alone…Screenings used to just involve IOP checks, but now they have been extended to include visual function testing and possibly an examination of the optic nerve, but that ups the cost per diagnosed case to about $1,500 – and you can't spend that much to screen the population...If we were doing a perfect job and had 95% of glaucoma patients under treatment with perfect compliance, then you could think of this as preaching to the choir, but we still have a long way to go in getting patients to stay compliant."

The website puts additional resources at doctors' fingertips. It contains the most current studies and data on glaucoma diagnosis, prevention, and long-term management; a patient checklist to help identify risk factors for glaucoma; and links to continuing medical education (CME), a library of landmark glaucoma studies, and the latest news. Dr. Cioffi said, "Last year Prevent Blindness's glaucoma advisory committee rewrote and updated all the fact sheets, and there are nearly a hundred on the website…There is CME on the site…And a subcommittee will pull the most pertinent articles (published about glaucoma) and put them on the website – either the abstract or a downloadable PDF.

Therapies

Allergan has been very successful in switching Alphagan users to Alphagan P, and doctors are remaining surprising loyal to Alphagan P even after the introduction of generic brimonidine. A source said, "The majority of doctors use Alphagan P because they used Alphagan, and they just didn't go to the generic. Change (to generic) will be hard because once doctors change it is difficult to get them to think about changing back – unless the price is significantly lower. However, I think Alphagan P use will go down over the next year."

The prostaglandin marketing wars among Pfizer's Xalatan(latanoprost), Alcon's Travatan (travoprost), and Allergan's Lumigan (bimataprost) continue. Soon there will be competition in combination products (prostaglandin+beta blocker) as well. Sources generally predicted that doctors will choose the combination product based on the prostaglandin-of-preference that it contains. That is, Xalatan users will opt for Xalcom, Travatan users will choose Extravan, etc.

Among the combination products approved or in development are:

- **PFIZER'S Xalcom** (latanaprost+timolol). The company got an approvable letter in October 2001, but the FDA wanted additional studies, and Xalcom is still awaiting final approval. Several sources were dubious that it will ever get approved. One commented, "I'm not sure this will ever get approved."

- **ALLERGAN'S** bimataprost+timolol. The brand name of this has not yet been announced. It was filed with the FDA in November 2003.

- **ALLERGAN'S Combigan** (brimonidine+timolol). This combination is currently available in Canada and has been under review by the FDA since September 2001. Interestingly, the studies of Combigan found fewer side effects than with brimonidine (Alphagan) alone; Combigan was not compared to Alphagan P. A glaucoma expert said, "This is not as good as the other combinations. It will be seldom used."

- **ALCON'S Extravan** (travaprost+timolol). A glaucoma expert said, "Extravan holds the most promise. It works the best." New, three-month data on Extravan were presented at ARVO, and it showed the combination lowered IOP about 2 mm more than either travaprost (Travatan) or timolol alone.

Alcon also presented preclinical data on AL-12182, a prostaglandin analog with "outstanding efficacy and a low propensity for hyperemia."

IOP Measurements at 90-Days in Extravan Trial

Time frame	Extravan n=82	Travatan n=84	p-value (Extravan vs. Travatan)	Timolol n=92	p-value (Extravan vs. timolol)
Baseline					
8 am	30.2	29.6	.228	29.3	.046
10 am	28.6	28.0	.161	27.9	.102
4 pm	27.2	26.6	.200	26.8	.398
Week 2					
8 am	-11.3	-9.1	<.001	-8.0	<.001
10 am	-10.6	-9.0	.018	-7.5	<.001
4 pm	-9.9	-7.9	.004	-6.7	<.001
Week 6					
8 am	-11.3	-9.3	.001	-8.7	<.001
10 am	-10.8	-8.8	.002	-7.9	<.001
4 pm	-9.2	-8.0	.077	-7.1	<.001
Month 3					
8 am	-11.5	-9.1	<.001	-8.5	<.001
10 am	-10.4	-8.7	.008	-8.0	<.001
4 pm	-8.8	-7.7	.122	-6.8	.002

ANTI-INFECTIVES

Among the ophthalmic fluoroquinolone choices doctors now have are:

- **ALLERGAN'S Ocuflox** (ofloxacin, 0.3%), a third generation agent.
- **ALCON'S Vigamox** (moxifloxacin, 0.5%), a fourth generation agent with no preservative.
- **ALLERGAN'S Zymar** (gatifloxacin, 0.3%), a fourth generation agent. Allergan has done a good job of converting Ocuflox patients to this. A researcher said, "Two-thirds of doctors have already switched from Ocuflox to Zymar. Most of the sales have been switches, not market expansion. By next year, most fluoroquinolone use will be fourth generation agents."

Comparison of 4th Generation Fluoroquinolones

Measurement	Zymar (gatifloxacin)	Vigamox (moxifloxacin)
Generation	4th	4th
Susceptible microbes	Gram negative	Gram positive
Tissue penetration	---	10x higher than Zymar
Dosing	TID for 7 days	Q2h up to 8 times a day for Days 1 and 2, then ≤4 times a day on Days 3-7
Marketing	---	Better
Labeling	6 organisms	22 organisms
Usage	Less derangement of epithelial barrier	Abnormalities of corneal epithelial tight juncture
Preservative	BAK	None
Clinical performance	Comparable	
Toxicity	Little higher	Patients report some stinging
Advantages	Works better for atypicals; Good for dry eye patients	Less corneal toxicity; Better wound healing; Excellent penetration; Less frequent dosing; Higher penetration

Each of the fourth generation fluoroquinolones has its supporters – Alcon's Vigamox (moxifloxacin) and Allergan's Zymar (gatifloxacin). A Midwest doctor said, "We use Zymar and Vigamox equally now, but we are thinking about whether we should shift to one or the other more heavily. We haven't decided yet, but it is under discussion." Another doctor said, "When efficacy is the same – and it is with these – then I look to limit side effects." A third doctor said, "The choice between Zymar and Vigamox tends to be formulary-driven. I'm comfortable with either." A Michigan doctor said, "For corneal ulcers, where frequent dosing is necessary, I use more Zymar. For corneal transplants and LASIK patients, I split use 50/50 between Zymar and Vigamox."

A Florida doctor is worried that over-use of fourth generation fluoroquinolones is already causing resistance to develop. The anti-infectives are part of the protocols for Macugen and Lucentis, cataract surgery, and LASIK patients. He said, about 10% of patients at his institution are resistant to Zymar and Vigamox, and he is worried about this increasing as the use of the agents increases.

NEUROPROTECTION

Current neuroprotection targets in glaucoma include:

- Caspase and semaphorin inhibitors
- NMDA receptor antagonists (e.g., memantine)
- Neurotrophin receptors with cytokine and growth factors

Current neuroprotective technologies in development include:

- Intravitreal injections
- Gene therapy
- Polymeric drug delivery, including biodegradable polymers

ALLERGAN

- **Memantine.** Forest Laboratories has the rights to memantine for Alzheimer's Disease, but Allergan has the rights for ocular disease. This could make marketing and pricing interesting, but an Allergan official insisted the company's hands are not tied in these areas by any contractual agreements (i.e., Allergan could price its product above or below Forest's Namenda).

Two Phase III trials of the neuroprotectivity of memantine are ongoing, and at least one is fully enrolled with "thousands" of patients. Allergan officials are being very tight-lipped about any other details of the status or design of that trial, but an official did say that "validated endpoints are being used," and another source said the trial enrolled ~2,000 patients. A researcher who worked on the animal studies said she is optimistic about the outlook for memantine in AMD, commenting, "It really works." She said it works in a dose-dependent manner, protecting retinal function against retinal ischemia.

Measurement	Saline	5 mg/kg	10 mg/kg	20 mg/kg
ERG* response post-ischemia (test/control eye)	20%	~18%	~30%	~57%

*electroretinogram

An Allergan official said:

- "The therapeutic window may be narrow for brain disease but wider for glaucoma."
- "Memantine did not decrease IOP in ocular hypertensive rats; its neuroprotective effects are independent of that."

- "It may take two to three years to prove that a neuro-protective drug is better than the natural history of disease…and we may get unlucky at 24 months and may need to go three to four years to show a benefit in neuroprotection. That is the big challenge in the clinic."
- "The FDA wants 'functional vision protection,' which means you need to wait years to see a difference between treated and untreated patients…Neuroprotection for glaucoma is probably going to take years."

➢ **Posurdex (dexamethasone).** A researcher reported on studies in macular edema of Posurdex, a bioerodable system of delivering dexamethasone encapsulated in a small bioerodable PLGA polymer pellet that can be inserted via a 22 gauge needle in a doctor's office. A researcher said, "This is true slow release, not triamcinolone." He reported on early data from a Phase I/II trial, "There were very few drug-related serious adverse events, and no endophthalmitis…Nor was cataract a problem with these patients, which is somewhat different from triamcinolone or fluorocinolone…There was a clear-cut dose response, and no significant safety concerns. Diabetics showed the most effect."

Subgroup Analysis of Posurdex in DME Patients

Measurement	Observation	350 µg Posurdex	700 µg Posurdex
Gain ≥2 lines of vision	12.7%	24.5%	34%
Gained 3 lines	1.8%	6.1%	13.2%

A prospective, controlled, Phase III trial of Posurdex as a neuroprotective for glaucoma will start in 3Q04. It will compare dexamethasone to sham. Allergan officials declined to give any additional details about the trial except to say that a new office-based insert is being used in that trial. A diabetic macular edema (DME) trial will follow.

MITSUBISHI PHARMA'S Radicut (edaravone)

This drug is already available in Japan for stroke neuroprotection, and a poster at ARVO reported on its neuroprotective ability in AMRD. A researcher said it is best when given by intravitreal injection. The human dose is 3 mg/kg, and a dose of 90 mg/kg was fatal to rats.

Measurement	Saline	15 mg/kg	22 mg/kg	45 mg/kg
% survival of RGC	28%	37%	44%	29%
p-value	---	.04	.001	.008

TEVA PHARMACEUTICALS' Copaxone (copolymer-1)

Israeli researchers reported on using Copaxone to "vaccinate" patients against glaucoma. They offered a mechanistic reason for low dose Copaxone to work as a neuroprotective. Based on animal studies, they reported that, instead of daily administration as for MS, Copaxone may only need to be given once every three or four weeks for neuroprotection. A speaker said, "I am not suggesting glaucoma is an inflammatory disease...(but) Copaxone vaccination is beneficial *in terms of function* in chronic glaucoma…We are still working on dosing…I think we can do it monthly and get a long-lasting effect…Vaccination with Copaxone retards/halts degeneration…This is not a way to prevent disease but a way to halt disease progression...In five years, I would hope to inform you that it works in patients." Copaxone also may be useful in head trauma, ALS, and Parkinson's disease.

Another researcher offered some other interesting comments about Copaxone as a neuroprotective:

- ➢ It works in acute glaucoma when given either subcutaneously or topically. When administered as eye drops, it doesn't penetrate the eye and is absorbed systemically.
- ➢ Daily injections are not effective.
- ➢ Copaxone is not a substitute for IOP lowering therapy.

Other neuroprotectives being investigated include:

- ➢ **Statins**, particularly lovastatin. A speaker said, "This might be ripe for study in glaucoma…Do patients on statins do better than those not on statins? There was a preliminary study at Duke, but we plan to do more studies, including a prospective study."
- ➢ **Erythropoietin.** Some studies presented at ARVO suggested erythropoietin has a neuroprotective effect for glaucoma. However, experts were not completely convinced, and further research is needed. If EPO is neuroprotective, the dosing and administration would still need to be worked out.
- ➢ **Minocycline**, a semisynthetic derivative of tetracycline. In rats, it did not prove neuroprotective at four days, but it did show a benefit at Weeks 1 and 2.
- ➢ **Nipradilol**, a topically administered beta blocker on the market in Japan.

OTHER DRUGS TO WATCH

Cox-2 Inhibitors

➢ **AMD.** A study at the University of Indiana reported that Novartis' Prexige (lumaricoxib) significantly decreased CNVM development in the rat laser-trauma model, suggesting that Cox-2 inhibitors may provide a benefit as a prophylactic inhibitor of CNVM formation in exudative AMD. Thus, if additional data support this, patients with AMD may want to consider starting a Cox-2. However, Novartis reportedly has put further clinical trials of Prexige in AMD – which are being done in the U.K. – on hold until the drug gains FDA approval for arthritis.

➢ **LASIK.** Some doctors are giving Cox-2 inhibitors for a few days (~3) prior to LASIK or PRK and a few days (~2) post-operatively.

Triamcinolone acetate

Interest in off-label use of triamcinolone acetate (Bristol-Myers Squibb's Kenalog) remains strong. Several retinal surgeons said they are using it successfully in combination with PDT. A California doctor said he adds Kenalog when CNV increases rather than decreases after the first Visudyne treatment. A Florida doctor said he has started using Kenalog routinely with PDT, "It seems to prolong the effect of Visudyne, and the fluorescein seems absolutely dry. I've had no problems with endophthalmitis or increased IOP."

One of the problems with Kenalog is the preservative, benzyl alcohol (BA). Several posters at ARVO pointed out the toxicity of BA. One poster reported transient toxicity in 1/3 of animals, even at a dose equivalent to a human dose, recommending that doctors remove the BA before using Kenalog by decanting it, pharmacologic washing, and filtering.

Allergan is working on getting FDA approval of triamcinolone for intraocular applications. The company's plan is to offer it in a pre-filled syringe, probably without BA. An Allergan poster reported that triamcinolone reduced intravitreal and subretinal accumulation of fluid produced by Visudyne in rabbits and monkeys. Researchers found that post-PDT dosing was effective in both species and that other types of pharmacologic adjuncts may be required to mitigate all the collateral damage from PDT.

Allergan will supply its novel ophthalmic formulation of triamcinolone for two National Eye Institute-sponsored clinical trials on macular edema. Under the agreement, Allergan will be responsible for all costs associated with drug development, manufacturing, PK studies, and regulatory filings. Allergan also will pay $1.8 million to the Diabetic Retinopathy Clinical Research Network to help cover the costs of the trials.

Two Japanese posters recommended using a "sandwich" approach to administration of triamcinolone. They reported that using both intravitreal and a posterior sub-Tenon capsule injection – the sandwich – is more effective than intravitreal injection alone.

A 65-patient (73-eye) study by researchers at Robert Wood Johnson Medical Center found that intravitreal triamcinolone, given a week prior to PDT, could improve the efficacy of PDT in eyes with a poor response to previous PDT. They concluded, "Triamcinolone acetate may enhance the efficacy of Visudyne in the treatment of CNVM and decrease the number of treatments required…The decreased permeability and reduction of subretinal fluid may allow Visudyne to more effectively close vessels…Similar results have been seen in other studies with simultaneous treatment…I had hoped to see greater benefit with pre-treating…There is a theoretical advantage to prior treatment...but it seems the results are pretty similar…I would consider pre-treatment with intravitreal triamcinolone acetate if the patient has a poor response to PDT and significant SRF…I would consider initially treating lesions that are suspected of responding poorly to PDT (occult lesion, predominantly classic lesion, large CNVM, etc.)...but I know some (retina) groups that treat everyone with triamcinolone."

Six-Month Results Combining Triamcinolone and PDT

Change in Vision	Pre-Treated Eyes (n=46)		Naïve Eyes (n=27)	
	PDT alone	Triamcinolone then PDT	PDT alone	Triamcinolone then PDT
Improved 2 lines	15%	20%	23%	15%
Same	70%	67%	54%	59%
Worsened by 2 lines	15%	13%	23%	26%
Worsened by 6 lines	0	0	0	0
Stable vision	85%	87%	77%	74%
Resolution of SRF	---	50%	---	59%
Less SRF/SRH	---	48%	---	37%
Same	---	2%	---	4%
Worse	---	0	---	0
Resolution of leakage by fluorescein angiography	---	52%	---	56%
Less leakage	---	39%	---	40%
Same leakage	---	9%	---	4%
More leakage	---	0	---	0
Required no further PDT	---	50%	---	59%
Required only one additional PDT	---	35%	---	---

DRUG DELIVERY

Helical screw. At ARVO 2003, researchers from Doheny Eye Institute at the University of Southern California reported on a novel drug delivery device that they were working on with SurModics, using SurModics polymer coating technology. It is a helical intravitreal implant, shaped like a corkscrew, that elutes triamcinolone. The device initially was made out of stainless steel with a uniform polymer coating (not bioerodable) that is 25-59 µm thick, but a non-ferrous alloy is now being used, and the thickness of the sprayed on coating has been increased to 50 µm.

The device can be implanted through a 30 gauge needle, is removable, and provides sustained release for about one year. To implant the device, the sclera is pierced, then the device "screwed" in.

Currently, a nine-month study of 40 rabbit eyes is ongoing. All 40 have been implanted and one-month follow-up completed. A researcher said, "This has been a 10-minute

procedure…The device is well-tolerated up to six months… There is a good elution rate…There has been little peri-device bleeding, a little tissue debris on the device tip (38% of cases), which is not surprising since we are pushing it through the sclera, and there is no coating on the tip. There has been mild hemorrhage in 18% of cases, no conjunctival redness at one month, and no thinning, migration, or fibrous growths. There has been an appearance of focal cataract in 18% of eyes, which we attributed to contact between the tip of the device and the lens, which is difficult to avoid in large rabbit eyes – it was designed for human eyes, and it is difficult to put the same device in a rabbit without hitting the lens…At four weeks post-op, there is no difference in IOP between the implanted and naïve eye."

Researchers plan to continue this safety study out to nine months and to do more in vivo elution profiles. However, a Phase I clinical study is planned to start enrolling in DME in late 2004.

HDP-cCDV. A researcher from Jacobs Retina Center in La Jolla reported on HDP-cCDV, a long-lasting, crystalline lipid prodrug of cyclic cidofovir to treat experimental retinitis. So far, it has been tested only in a limited number of rabbit eyes. HDP-cCDV has a longer half-life than cCDV and cidofovir (6 days vs. 10 hours for cCDV and 20 hours for cidofovir). All the animals maintained good general health; there was no observable systemic toxicity; and there was no clinically detectable toxicity, except for one eye which demonstrated a local cataract.

There were no IOP differences between injected drug and control eyes at any time points except for a drop at Day 3 after drug injection, which the researcher attributed to initial burst release, and all pressures returned to normal. All eyes demonstrated normal ERG waveform, indicating no electrographic toxicity. The researcher said, "Our study indicates there are 100 days of protection after a single dose injection, no intraocular toxicity except for possible local cataract (10%), and a high therapeutic index…This may be an ideal local, long-lasting slow release drug and a safer alternative to treat CMV retinitis by intravitreal injection at intervals of two to three months. This is a new type of long-acting intravitreal delivery system."

LASIK

Doctors have seen a pickup in LASIK procedures so far this year, but they are ***very*** hesitant to say how this will play out for the rest of the year. Over and over, doctors emphasized that LASIK volume is very sensitive to, and dependent on, the economy, consumer confidence, and the consumer price index. If the economy stumbles at all – which many doubt will happen in a presidential election year – it will depress LASIK demand. Sources also are not sure how a rise in interest rates will affect LASIK. Basically, they are indicating that the LASIK recovery is very fragile. A Minnesota surgeon said, "There is a slight pickup, mostly due to the economy. Patients are coming in who couldn't afford it before."

Pricing for LASIK among doctors questioned at the meeting ranges from $1,600–$2,100 per eye, with custom ablation – Visx's WaveFront, Alcon's CustomCornea, or Bausch & Lomb's Zyoptix/Orbscan – adding another $500–$1,000 per eye. This makes the cost of a custom procedure range from $2,100–$3,100 per eye. Most doctors are continuing to have dual pricing – one price with custom ablation and another without it, but some doctors have decided to charge the same fee whether patients get custom ablation or not. One source explained, "We wanted patients to get what was best for them, not pay for something they didn't need or avoid something they did because of the cost. So, in January 2004 we went to a flat $2,700 per eye."

The outlook is for custom ablation as a percentage of LASIK procedures to continue to increase, but there appear to be two camps forming on custom ablation.

- **Positive**. This group raves about it and the outcomes.
- **Negative**. This group claims custom ablation adds cost without really providing any benefit. Researchers at Ohio State presented a study of 2,752 patients that found custom ablation does not improve outcomes – at least in terms of night vision symptoms or dry eye – in low myopes (≤-6 diopters), except that there may be fewer halos with custom ablation. However, a researcher said surgeons there are still doing customer ablation in lower myopes. A Pennsylvania doctor said, "I'm up in the air on custom ablation. You get 2% better vision for 20% less efficiency. There is a learning curve with it, and the cases you most want it for you can't use it in." A New York doctor said, "It is just an expensive auto refractor." Another doctor said, "The Alcon system has a real difference, but the Visx WaveFront does nothing; the math isn't there. And that could cause a backlash against Visx…At first I advertised (my Visx WaveFront), but I stopped."

The military offers soldiers free laser vision correction but does mostly PRK. In part, this is because only PRK is approved for pilots, because flaps can be a problem in sandy environments, etc. A military doctor said there is strong support for laser vision correction in the services. He said contact lenses in an unfit environment lead to complications that are avoided with laser vision correction.

Measurement	Incidence during Desert Storm	Incidence during first year of Iraqi Freedom
Open globes	68 patients	~68 patients
Corneal ulcers	500 patients	160 patients

However, military doctors do perform some LASIK. One military base has started a study of custom ablation LASIK vs. PRK, and those results should be interesting when they are available – perhaps at ARVO 2005.

Lasers

Nikon and Osaka University in Japan presented preliminary data on a newly developed 193 nm solid state laser for LASIK, which a researcher described as "possibly the next generation laser for LASIK." He said it could be better than the excimer laser currently used because it would avoid these problems with excimer lasers:

- Long pulse duration and low repitition rate.
- Use of toxic gas.
- High maintenance costs.
- Difficulty in improving beam quality and stabilizing the power.

NON-LASIK VISION CORRECTION

Clear Lens Exchange

One surgeon said he is using Pfizer's Technis lens (which was recently sold to AMO) for clear lens exchange with good results. Another expert described the AMO Array as "not a very good lens." He is currently doing clear lens change, but not with the Array, and he doesn't plan to start using the Array for that.

However, this same expert was surprisingly positive about Alcon's AcrySof ReSTOR lens, an accommodating IOL. He predicted that ReSTOR will be the best thing yet for presbyopia when it gets approved for clear lens exchange, and he was confident that will occur. ReSTOR was approved in Europe in April 2003 and is expected to be available in the U.S. in 2005. Data from a 760-patient, U.S./European Phase III trial were presented after ARVO at the American Society of Cataract and Refractive Surgery (ASCRS) annual symposium in San Diego.

Phase III ReSTOR Trial

Measurement	AcrySof ReSTOR n=566	AcrySof monofocal IOL n=194	p-value
Distance VA ≥20/40 without contacts or glasses	99%	98%	Nss
Distance VA ≥20/25 without contacts or glasses	88%	92%	Nss
Near VA ≥20/25 without contacts or glasses	74%	14%	p<.05
Functional binocular uncorrected intermediate vision (≥20/40 J3)	85%	67%	p<.05
Never used glasses for near or distance vision	80%	8%	p<.05
Contrast sensitivity	No clinical or functional difference		---

AMO has a new lens coming out, ReZoom, and several doctors praised it. One said, "There are fewer halos, better near vision, equal distance vision, and a little less middle vision. It will be a good lens."

Phakic IOLs

➢ **STAAR SURGICAL'S Visian ICL.** There wasn't much news or discussion of this product at ARVO. One surgeon warned, "I think Staar's Visian will cause cataracts. I've done it, and it is hard to do, like AMO's Verisyse (also to be sold by Ophtec as Artisan). There is no way to properly size the angle. All phakic IOLs work, but they are a pain to use."

➢ **AMO/OPHTEC'S Verisyse/Artisan**

Several doctors who have worked with this implantable contact lens (phakic IOL) said it is very difficult to implant and will not be able to be used by the average ophthalmologist or even the average refractive surgeon.

REFRACTEC'S Conductive Keratoplasy (CK)

This product may do better than previously thought. While doctors who are doing CK did not predict much procedure growth over the next year, a number of doctors said they are thinking about starting to do CK. And there do not appear to be any serious competitors on the horizon. One prominent ophthalmologist commented, "I think I'm going to have to spend the $50,000 and get this. Patients are asking for it. I don't think the effects last very long, but I can't not offer it." Another said, "There will be more CK growth for off-label indications. You can't live without CK in a cornea practice." A third said, "It might become part of the culture."

On the other hand, a New Jersey doctor who participated in the CK pivotal trial and who currently is doing a fair amount of CK for post-cataract and post-LASIK patients said CK is not as good post-PRK as post-LASIK. Asked about sub-sidence, she said they brought back as many of the original 72 patients from the pivotal trial as possible (actually they got 24), and the patients are "holding pretty strong." She said there is more near demand (more presbyopia), but she thinks that is normal presbyopia progression, not CK regression. According to this expert, the best patients for CK are myopes with an initial over-correction rather than an under-corrected hyperope. She said older hyperopic females with 20/30 vision, not male 45-year-old golfers, are the best patients.

Side effects of CK include glare, halos, and induced astigmatism. A surgeon commented, "There is some against-the-rule astigmatism that relaxes over the first month, but there also is some induced astigmatism…The biggest problem with CK is that you don't get enough treatment effect." Another doctor said there have been three case reports of the CK "plug" being pulled out during LASIK done post-CK.

♦