Trends-in-Medicine

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By Lynne Peterson

SUMMARY

LASIK volumes are up year-over-year, but have not returned to pre-September 11th levels, and the outlook for 12%-15% more procedures in 2004 than 2003. Custom cornea has really caught on, but many doctors are not convinced it improves outcomes. ♦ Non-LASIK vision correction options – conductive keratoplasty, phakic IOLs, clear lens exchange, etc. – are getting a lot of attention. ♦ The new AMD drug closest to market appears to be Eyetech's Macugen. Pooled data from 2 Phase II/III trials indicated Macugen is effective, safe, and works in all lesion types. Questions were raised about the pooled analysis, but if Macugen gets FDA approval, sources expect widespread use both as monotherapy and in combination with QLT's Visudyne and other future agents. ♦ Bristol-Myers Squibb's Kenalog continues to be widely used off-label to treat AMD, uveitis and macular edema.

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AMERICAN ACADEMY OF OPHTHALMOLOGY

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This meeting was well-attended, from the first subspecialty day to the last lecture. There was news in almost every field of ophthalmology, but this report focuses on trends in LASIK refractive surgery, new implantable lenses and procedures for non-LASIK vision correction, and new agents to treat macular degeneration.

LASIK REFRACTIVE SURGERY

LASIK continues to be the refractive procedure of choice for most doctors and patients, but procedure volume has never recovered from the hit it took post-September 11th. Doctors said their December bookings had taken the usual seasonal fall, but were still up a little over 2002. January 2004 was looking as if it would be up over December, but no sources expected January to be a "blow out" month. A Colorado surgeon said, "January is busy." A Tennessee surgeon said, "January looks good because of flex spending plans. Patients are holding off to do two eyes in January. January will be the biggest month of the year."

The growth in procedures is due mostly, sources said, to custom cornea (wavefront), but the outlook for 2004 will depend on the economy more than custom cornea. A Washington D.C. doctor said, "The pickup is due to custom cornea. It is the new buzz." A Georgia doctor said, "Wavefront is now a model T. In the future, it will improve and then become the standard o care. This is versions 2.0 in refractive surgery, so I think there is a modest interest increase." A Washington surgeon said, "The custom cornea bolus is over. People are waiting for something (else) new, and to work out the kinks." A Texas doctor said, "If custom cornea has a benefit in terms of patient outcome outside of clinical trials, it will increase, but it is not perfect."

LASIK Procedure Volume (Year-to-Year Change)

Expert	2003 Estimate (year-to-year change)	2004 Estimate (year-to-year change)	2005 Estimate (year-to-year change)
Dave Harmon MarketScope	1.2 million (+2%)	1.35 million (+12.5%)	1,450 (+7%)
Irving Arons Spectrum Consulting	1.35 (+12.5%)	1.553 (+15%)	1.785 (+15%)

Most refractive surgeons either have custom cornea capability or are adding it – and it is affecting their choice of laser to buy. However, very few doctors

indicated any plans to purchase a new laser, and there appeared to be little interest in B&L's Technolas 217. A Massachusetts doctor said, "Wavefront is important in the choice of a laser. Visx, Alcon, Nidek and B&L are all about the same. I wouldn't try a Nidek now because it doesn't have custom cornea."

Most sources are raising their overall price or charging patients extra for custom cornea; few surgeons are eating the cost themselves. There were a few reports of increased activity by discount laser centers, but most doctors did not see this as a major issue now or for the near future.

Rumors have started that there may be differences in the outcomes of the various wavefront systems. The January 2004 issue of EuroTimes reported on a study that compared the leading LASIK systems, and differences between wavefront aberrometers were found, both in how they measure and what they measure, suggesting this could result in different clinical outcomes. At the European Society of Cataract and Refractive Surgeons (ESCRS) meeting in Munich, researchers from Magill Research Center's Storm Eye Institute discussed the design and early findings of a prospective, randomized clinical trial they are conducting of several available systems for conventional and customized LASIK. The study will involve a total of 120 eyes of 60 patients undergoing conventional LASIK with either Alcon's LADARVision, B&L's Technolas 217z, Visx's S4 (VISX) systems, or custom ablation with Alcon's CustomCornea, Visx's CustomVue, or B&L's Zyoptix.

According to the EuroTimes report, the principal investigator reported preliminary results (in only a few patients) that showed an apparent benefit (fewer HOAs at one-month, greater contrast sensitivity, and better driving vision) for custom over conventional treatment when comparing the two Alcon systems. However, the investigator did not find a reduction in HOAs with the Visx CustomVue, though conventional LASIK with the S4 seemed to induce less HOA than conventional treatment with the Alcon LADARVision.

Company	Product	Comments
Phakic IOLs (also known as ICLs)		
Alcon	AcrySof	FDA approved in October 2003
Novartis/CIBA Vision	Vivarte	Anterior Angle fixated
Novartis/CIBA Vision (purchased from Medennium)	Phakic Refractive Lens (PRL)	Posterior Silicone, hydrophobic Floats on the aqueous humor without \ touching the anterior surface of the lens
Ophtec and AMO	Artisan/Verisyse	Anterior chamber Iris fixated Technically difficult but reversible
Staar	Visian ICL	Posterior chamber Only FDA-approved ICL Acrylic, hydrophilic
Accommodating IOLs		
Alcon	AcrySof ReStor	Pseudo-accommodative Bifocal lens – good for large pupils but may have problems with computer screen vision
Calhoun	N/A	Light adjustable
Eyeonics (formerly C&C)	Crystalens	Hinged Approved only for cataracts Accommodative
Medennium	SmartIOL	Injectable, full-size, accommodating IOL
Other Lenses for Refractive Lens Exchange		
Alcon	AcrySof Toric	In clinical trials Cataract lens for astigmatism
AMO	Array	Multifocal IOL Only approved for cataracts in U.S. Approved to treat presbyopia in Europe
Pfizer/Pharmacia	Technis	Aspheric Modified (wavefront) prolate surface Traditional cataract implant
Staar	ICL Toric	Corrects astigmatism Spheric and cylindrical correction
ThinOptx	UltraChoice	Extremely thin IOL that can be rolled up and inserted through a very small incision

NON-LASIK VISION CORRECTION

Interest in alternatives to LASIK for vision correction -- e.g., conductive keratoplasty, phakic IOLs, clear lens exchange -- is growing. There was even a suggestion that cataract and refractive surgeries are merging, with cataract surgeons who have not gotten into LASIK refractive surgery now showing considerable interest in some new technologies. In line with this, refractive surgeons asked at AAO about some of these non-LASIK procedures and products showed little interest in most of them. However, many cataract surgeons who never got into LASIK commented that they are thinking about trying one or more of these alternative procedures. An expert said, "Cataract surgery is evolving into refractive surgery…LASIK doesn't address high myopes, high hyperopes, and it is questionable whether it will ever address presbyopia."

Which of these procedures is most likely to grow? A source said, "Most patients are low to moderate myopes or hyperopes with a moderate astigmatism, so corneal procedures – LASIK, etc. – will continue to dominate. The other procedures are more niche applications where LASIK is less attractive. For example, for higher nearsighted patients, a phakic IOL is very good. But for farsighted patients, a phakic IOL is a big challenge, and the one people think will work best is a refractive lens exchange, so you will see a lot more of that…CK is really ideal for presbyopes with good near vision in one eye; if patients are good candidates for monovision, then CK is very attractive for them…Capsular refilling for presbyopia has enormous appeal in theory, but there are tremendous challenges, including a tendency to opacify. We

are making very slow progress down that road. A surrogate for that is a kind of jelly-like substance that expands, and that has the potential of filling the bag and expanding. That ultimately can get us in that direction even though it is not the same as an injectable polymer."

The variety of new procedures and options available today can be confusing for doctors as well as patients, sources said. Thus, many doctors are choosing one or two vision correcting services to offer patients, not the whole array. A Midwest doctor said, "All that patients know is that they have a visual problem, and they want an ophthalmologist to tell them their options…There is a lot of confusion and a need for continuing education that we and the (ophthalmology) societies are addressing…The more new technology comes along, the more bewildering it is…The Eye Surgery Education Council (eyesurgeryeducation.com) was formed, geared to lay people, and there will be a big public education effort…In our office, we make an assessment, and provide one or two recommendations. We won't bewilder patients with too many options."

Accommodative Lenses

An expert predicted that accommodating IOLs will be the "new paradigm." He said, "All of the major manufacturers are working in this area…And many follow-ons will be even better than existing products…This (Eyeonics' Crystalens) is the first technology of which I'm aware that I think is good and won't be available to my Medicare patients…If the first diagnosis is presbyopia, the patient will pay for it. If the diagnosis is a cataract, and if the patient pays the difference from the cost of a standard IOL, I find carriers will pay…If a patient has a cataract, and I'm a Medicare participating physician, it is illegal for the patient to get this. I can't provide this to Medicare patients unless I do it at no additional charge -- and the company (Eyeonics) is charging more than the $150-$200 Medicare will pay. So, it is not available to our seniors…I hope there are changes to Medicare in the future so patients can pay for superior technology."

Multifocal IOLs for Presbyopia

The advantage to multifocal IOLs for presbyopia is that they provide two focal ranges at the same time. The disadvantage is that contrast sensitivity is somewhat compromised. An expert said, "Multifocal IOLs should work for everyone, whereas only two-thirds of patients are able to adjust to monovision, in which one eye is corrected for near vision and the other for distance."

Refractive Lens Exchange (also called clear lens exchange or clear lensectomy)

An expert predicted refractive lens exchange with IOLs will become the dominant refractive procedure, calling it a win-win-win" solution. He said, "It reduces the number of patient problems for surgeons, and it even benefits the government because there will be a dramatic decrease in the expense of cataract surgery."

Some doctors said they were horrified at the idea of replacing a healthy lens, but other doctors find it a good option, especially for hyperopes. An expert said, "I just talked with the past president of ASCRS (American Society of Cataract and Refractive Surgery), and he had bilateral Array lenses…He is a pilot and he operated a couple days after his surgery...He is happy, but he has 'learned to love halos' instead of presbyopia…So there are patients who want that." Another expert said, "The reason the name 'refractive lens exchange' was chosen is that most patients don't come in knowing that this procedure is for them…They come in looking for refractive surgery."

Following are comments on specific products:

ALCON'S AcrySof ReStor

This diffractive bifocal IOL is not yet FDA-approved. An expert said it is good for patients with a large pupil, but there is some concern about its utility with computer screens.

AMO'S Array (SA-40NB)

The best patient acceptance reportedly is in hyperopes. The downside is some loss in contrast sensitivity.

EYEONICS' Crystalens

Crystalens received FDA approval for cataract patients during the AAO meeting, but sources said there would be little usage until it is covered by Medicare. Crystalens is the first accommodative IOL – an IOL designed to restore both near and far vision. It is a modified plate haptic lens with hinges connecting two plates on the sides of the lens. The lens and plate parts are made of silicone and are held in the eye by plastic loops.

CALHOUN VISION'S Light adjustable Lens (LAL)

This lens can be adjusted for two to three weeks after implantation. It uses a Calhoun-Zeiss Digital LDD laser (digital light delivery), has the capacity to refine vision to higher levels (better than 20/20) and can produce sharp, clear quality. Phase I clinical trials are due to begin in early 2004. A speaker said, "The company is now working out the technical details on how to deliver the laser energy, but that seems to be working now. For the U.S., this is probably three years away."

MEDENNIUM'S SmartIOL

In March 2003, Medennium sold the PRL to Novartis's Ciba Vision, and is now focusing on the Smart IOL.

MORCHER'S Capsular Tension Ring (CTR)

In October 2003, the FDA approved this endocapsular ring. The Capsular Tension Ring is a sterile, non-optical ocular implant that is permanently inserted into the crystalline lens capsular bag during intraocular lens surgery. The device acts to stabilize the capsule in the case of damaged or missing supporting zonules by circularly expanding the capsular bag. The Capsular Tension Ring is a circular ring, approximately 0.2 mm in cross-section, interrupted by positioning hole ends, and made of ultraviolet light (UV)-absorbing polymethyl-methacrylate (PMMA). A CTR allows surgeons to reduce the size of the pupil in patients with a defective iris due to birth defects or trauma. It also can be helpful in reducing glare. Morcher implants have a CE mark and are widely used in Europe, but they have been available in the U.S. only through an FDA compassionate device exemption.

NOVARTIS/CIBA VISION/MEDENNIUM'S PRL

A speaker commented on this lens, saying, "I particularly like this…It converts at room temperature to a small rod, and then body temperature expands it to full size…It totally fills the capsular bag, so there is no edge effect possible, no glare…And there is a high amplitude of accommo-dation…This is extremely important new technology."

OPHTEC'S Artisan (to be sold by AMO as Verisyse)

Artisan/Verisyse, an iris-fixated ICL, is already sold in Europe (with dual branding), and it will be considered by an FDA Advisory Committee in February 2004. It was filed with the FDA in July 2003 and granted expedited review. In the trials, patients were eligible with –5 to –20 but surgeons typically use it for patients in the –8 or higher range. An investigator said, "I started doing –12 patients, but now I do patients in the –7 range because I get better results than a laser in those patients." This doctor, who has his own ambulatory surgery center (ASC) charges $2,600 per eye for Artisan implantation.

The advantages are:

- Reversibility.
- Outpatient procedure.
- Wide range of powers (-3 to –24 diopters and +1 to +12 diopters)

Concerns with this device include:

- Endothelial cell loss over time.
- Cataract formation.
- Expertise needed. An investigator said, "I've been doing this for six years with none of the patient complaints I get with LASIK patients. But it requires a very good surgeon." He said surgeons need to be able to use their left hand for the surgery – not just hold an instrument with the left hand, but actually use it – and that can be difficult.

PFIZER/PHARMACIA'S Technis Z9000 IOL

This non-spherical lens allows light to focus perfectly on the retina, thus restoring contrast sensitivity and nighttime vision. Several sources described this as the most exciting IOL. An expert said, "This lens is the biggest improvement in optical design since we added UV back in the 1980s…This lens actually had the biggest increase in sales in last six months of any lens developed in the U.S."

REFRACTEC'S Conductive Keratoplasty (CK)

Refractec's ViewPoint CK System has been catching on slowly, and that does not appear to be changing. Since CK was approved in April 2002, about 400 doctors have been trained and more than 20,000 procedures have been done in the U.S. It is FDA-approved to treat spherical hyperopia (+.75 to +3.25 D), but the real interest is in the off-label use for treatment of presbyopia.

CK uses radiofrequency (at 350 KHz) to heat tissue in the stroma and create a deep stroma collagen contraction in the treatment spot. A cylindrical footprint ~80 mm deep – like a fencepost – is created. The system costs about $50,000 plus disposables of $1,000-$1,500 per eye. A speaker said, "In some ways I like to think of this as a corneal shape optimizer…the effect can be modified to plan for a reduction in presbyopic symptoms without inducing significant myopia…I'm more excited about this than LASIK monovision because the disparity between the two eyes is minimized. The presbyopia trials are still ongoing…but safety looks good."

Doctors at AAO were looking at CK, and lectures at the Refractec booth were filled, but most sources aren't ready to jump in. They are concerned with the cost of the machine, the duration of the effect, and the potential for creating irregular astigmatism. A doctor who performs CK said, "We offer a half price option for patients who want to have this done again in four or five years…At two years out I've seen about 1% of 700 cases who were losing some effect…They tend to be the younger patients." He advised doctors who are considering CK to create a non-surgical setting: "These patients don't want a laser aimed at them…They are used to going to Wal-mart for reading glasses…You should use a more causal room with carpet."

Following are some of the comments doctors made about CK:

Pro

Speaker: "Fifty-year-old myopes are good candidates. Some surgeons are doing LASIK in one eye, and this in the other."

Colorado: "It may have an excellent benefit, but I'm approaching it very slowly. There was LTK (Laser Thermokeratoplasty), and we had that for a year. It is now an expensive doorstop."

Massachusetts: Not many doctors are doing this yet. I'll do it initially on a few patients and see what results I get."

Con

New Mexico: "I have no interest in CK…It is beating up on the cornea."

Washington, D.C.: "We need more data first."

Florida: "That a monovision procedure, and I don't do it."

Georgia: "I don't do it. There is a fair amount of regression. It works short-term, but long-term there's too much regression."

California #1: "I tried it in Tijuana, Mexico. I'm not sure about it, especially for presbyopia. I prefer LASIK monovision."

California #2: "I'm not interested after LTK. I want to wait and see how it does. The LTK machines have turned into very expensive paperweights, and the question is whether CK will go the same way. The potential for regression and induced astigmatism is very high. LTK regression was in years 4 and 5."

Mixed

Indiana: "I'm skeptical. The company calls it 'blended vision,' but it's really monovision. However, I haven't closed the door on this."

Colorado: "I'm considering it. It might be good for patients age 45-70 with good distance vision but need reading glasses. But it has some of the feel of RK, and it could increase astigmatism."

Tennessee: "I might start doing it because I've seen a case with very good results. You can re-do, and it isn't permanent. I won't buy the system, but I would refer patients. Patients need good distance vision without glasses to be eligible. It might be good for selected patients."

STAAR SURGICAL'S Visian ICL

Staar facilities were inspected by the FDA in August and early September 2003, and then in December 2003, Staar received an FDA warning letter charging the company with failing to analyze and report product complaints involving blurred or cloudy vision and other factors for its ICLs. The FDA also raised questions about the validation tests of both raw materials and finished devices. Staar acknowledged that it needed to improve its reporting procedures. After a two-hour meeting with the FDA in January 2004, Staar officials said the company has "much work to do" before it can request a re-audit but said they were pleased with the progress to date. They said Staar will continue to implement corrective actions for the issues raised in the warning letter while waiting for an FDA response to the company's corrective action plan. The FDA concerns must be resolved before Staar can get any new device (including Visian) approved, but Staar is unable to put a timeframe on resolution of the FDA concerns.

An FDA advisory panel recommended the agency approve Visian for the correction of myopia. Though the recommended range is –3 to –20 diopters, the typical patient will be about –8 or higher, sources said. An expert estimated that about 1%-2% of the myopic population or 4%-6% of the entire U.S. population would be eligible for these devices – mostly patients who are not good LASIK candidates due to thin corneas.

The concerns doctors had with Visian are:

- Cataracts. Some patients (2.8% in one trial) developed a mild cataract as a result of the surgery, though a speaker said this is "not always visually significant."
- Corneal damage. There is some endothelial cell loss, and if that is progressive, it could lead to decompensation of the cornea, so the cornea needs to be monitored.
- Inflammation or irritation to the back surface of the eye.

Implantable Miniature Telescope

This device provides AMD patients with a 60% field of vision as opposed to only 20% with an external telescope. The IMT is currently in Phase II clinical trials. A small (15 patient) Phase I trial found that 77% of patients achieved an improvement in central vision of two lines, and 62% achieved an improvement of three lines. The concerns are: (a) the difficulty of examining the retina through the implant, (b) how to treat new bleeds, and (3) retinal detachments.

AGE-RELATED MACULAR DEGENERATION

Combining therapies may be the way to go in the future. An expert suggested, "Perhaps anecortave and then a laser, or PDT (Visudyne) plus Kenalog…so we are considering PPP: pharmacologic treatment, pause, then phototherapy. Or RAP: first a thermal laser, then PPP, then PDT." Another expert said, "Combination therapy is likely the trend in the future…but right now there are no good studies to conclusively demonstrate that combination therapy works and if so, which you should use…I think most of us anticipate that, down the road, we will have a regimen of treatments similar to chemotherapy where patients get combinations at different time intervals that are sequenced to match the cell cycle, capillary growth, leakage, etc…You might start with an anti-VEGF to shrink the membrane…and then follow with PDT to damage the cellular supply, and then give a steroid to stop leakage."

ALCON'S Retaane (anecortave)

There was no new data at the AAO meeting on this. Enrollment was completed in August 2003 for the 530-patient pivotal Phase III trial vs. Visudyne, and results are expected by AAO 2004. A European confirmatory study is underway, and a 2,500-patient CNV risk-reduction trial is due to start in January 2004.

Questions have been raised about whether the pivotal trial is adequately blinded. An investigator said, "When you inject anecortave you can tell by the consistency what you are injecting, so the injector knows, but he is not supposed to tell the patient."

Shortly after the AAO meeting, Alcon announced it was initiating two new, Phase III anecortave trials, studying whether it can slow progression from dry to wet AMD. The four-year trials will compare anecortave to placebo in about 2,500 patients world-wide. Alcon also said it has been granted fast track status for anecortave for that indication.

An anecortave+Visudyne trial is scheduled to start in 2004. A source said the thinking is that anecortave could be a "booster" for Visudyne.

EYETECH'S Macugen (pegaptanib sodium)

The Phase II/III data from two Phase II/III trials were presented at the Retina Specialty Day at AAO, but the speaker was allotted only five minutes, so it was a very condensed presentation. The blanks were mostly filled in later through interviews with investigators and from an EyeTech/Pfizer-sponsored breakfast session. ***Only the pooled analysis was presented***, but Macugen looked safe, effective and FDA-approvable in that data. The treatment effect – about 15% compared to sham – is comparable to the effect shown in other trials by Visudyne over placebo. 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 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."

Pooled Analysis of VISION Trials

Measurement	All Macugen patients	Sham (standard of care)
Drop-outs	8% *	8% *
Mean injections (maximum possible was 9)	8.4	8.6
Predominantly classic	27%	27%
Minimally classic	35%	35%
Occult	38%	38%
Mean age	76.0	75.7
Serious Adverse Events		
Endophthalmitis	12 patients (0.16% per injection)	N/A
Lens damage/cataract	5 patients (0.07% per injection)	N/A
Retinal detachment	4 patients (0.05% per injection)	N/A
Deaths	2 patients	2 patients
Mean Visual Acuity Loss from Baseline (in letters) **		
Predominantly classic (n=148, which is 27% of the patients in the trials)	~ -7	~ -14
Minimally classic (n=211)	~ -7	~ -14.2
Occult	~ - 9	~ -16.5

* One-quarter of these died

** On average, Macugen patients lost 1.5 lines of vision vs. 3 lines of vision loss for each sham group.

Pooled Analysis of Vision Trials

Vision	All Macugen patients	Sham (standard of care)	Change	p-value
Better by ≥ 0 line	33%	23%	43%	.0032
Better by ≥ 1 line	22%	12%	83%	.0043
Better ≥ 2 lines	11%	6%	83%	.0239
Better by ≥ 3 lines	6%	2%	200%	.0401
Worse by ≥ 6 lines	10% at .3 mg	22%	55%	<.001

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

Of course, the FDA will require each of the trials to meet the primary endpoint. However, investigators and company officials insisted those analyses were not finished yet, and they did not know the results of the individual trials. They also could not say when that data will be available, and they made no promises to present it at the Macula Society meeting in Las Vegas, February 25-28, 2004. A company official commented, "The data will be published sometime."

These Macugen trials were randomized, double-masked, 54-week studies (the Phase II/III EOP1004E and the Phase III EOP1003) with a total of 1,186 patients from 117 centers, with all angiographic subtypes of AMD included. The trial compared Macugen, an anti-VEGF pegylated aptamer, at three doses (0.3 mg, 1.0 mg and 3.0 mg, administered once every six weeks by intravitreal injection) to sham. Sham patients were given standard of care, which meant that >90% of patients with predominantly classic AMD got QLT Therapeutics' Visudyne (verteporfrin).

Among the key points researchers made about Macugen as a result of these trials:

- **The Macugen benefit is independent of lesion subtype**. There was less vision loss than sham with Macugen regardless of whether the patient had predominantly classic, minimally classic or occult AMD.

- There was **no dose response curve**. The 0.3 mg/kg dose is the dose that will be submitted to the FDA. The lack of a dose response curve was not concerning to investigators, who said it simply shows that 0.3 mg is enough. One commented, "This shows all the doses work – unlike anecortave."

- **The results were not analyzed by lesion size**, but the trials included lesions ≤12 total disc areas, which is a very large membrane. By comparison, the Visudyne TAP and VIP trials limited patients to ≤9 disc areas. A Macugen investigator estimated that about 10% of new patients have large lesions (≥6 discs), and he said there is a large pool of existing patients with large lesions.

- Most of the **endophthalmitis** occurred at a couple of sites, and investigators believe the true rate after the learning curve is considerably lower than 0.16%, but not zero.

- Macugen appears to **work in combination with PDT**, based on the results of the predominantly classic patients, most of whom got PDT. In contrast, Alcon's Retaane (anecortave) does not appear to work in combination with PDT. An investigator said, "I see a combination of Macugen and PDT as the future therapy." This doctor said that -- if Macugen were approved -- he would "continue to use PDT in predominantly classic patients, but patients with occult and others – especially those with big lesions – can get an immediate effect from Macugen."

- **How does Macugen compare to Genentech's Lucentis** (rhuFAB-V2). The mechanism of action of Macugen is similar to Lucentis, but a Macugen investigator claimed Lucentis causes more inflammation. He also predicted that Genentech may have trouble with enrolling patients or with dropouts in Lucentis trials once Macugen is approved, commenting, "I suspect Lucentis will be effective, but it may be difficult to prove." Another investigator said, "There may be subtle differences between the way Macugen produces effects and the way rhuFab does, but they will behave in a similar way...There could be toxicity and bioavailability differences, but in mechanism of action and inhibition of angiogenesis, they are similar."

- **How many doses will be needed in Year 2?** In year one, patients got an average of 8.4 of a possible 9 injections, but an investigator said he expects the drug to be given much less frequently in Year 1 once it is approved (outside a clinical trial), and he thought that it might be given only once in Year 2. He commented, "At the first re-treatment point, most patients would get another injection of Macugen, but then we would use angiography, clinical examination, and ICG. On questionable patients, I'd also do OCT."

- According to a source, the **FDA wants harder criteria** in each trial than a $p<.05$ value for approval of Macugen, but it appears the 0.3 mg dose meets that criteria. He didn't specify what the harder criteria area. He speculated that Macugen may not have met the primary endpoint for all other doses in both trials. A Macugen investigator said, "My opinion of Macugen would be weakened but not blown away if the primary endpoints for the other doses in each trial were non-significant."

- If Macugen is approved, sources expect it **will be used by some general ophthalmologists** as well as retinal specialists. In comparison, Visudyne is administered almost exclusively by retinal specialists.

An investigator cited three advantages to Macugen over other AMD agents in development:

1. **Broad efficacy.** He said, "I think Macugen has broader efficacy than anything else out there. It is not limited to one angiographic category, which suggests a favorable use profile compared to other agents, so that is a relative advantage."

2. **Cost.** He said, "It is more inexpensive than Visudyne…I can't comment on price, but I would say that if you look at practice economics, what it costs an office in terms of human and financial resources to administer Visudyne – and consider other parts of the world that have no access to PDT lasers, nurses, etc. This is relatively easy therapy to administer, and so I think it will be viewed favorably by the marketplace."

3. **Mechanism.** He said, "This is a drug that fundamentally addresses the basic pathophysiologic mechanism of the disease rather than just the later stages of the disease…You want to use drugs as far up river as possible because they tend to work better than drugs downstream…And we will learn a lot in the after-market about how this drug works…People will push the envelope, which I think personally is a good thing…And my prediction is that when it is used on patients with small lesions very early…it will probably have even more efficacy than it does in patients with big, hairy lesions with a lot of fibrosis and mass…My guess is it will look better and not worse as time goes by."

GENENTECH'S Lucentis (ranibizumab, rhuFAB)

There also was no new data at the AAO meeting on this anti-angiogenesis agent. Enrollment is nearly complete in both the Phase III trial (Study 2598) of 720 minimally classic/occult AMD patients and a head-to-head study vs. Visudyne (Study 2597).

MIRAVANT'S SnET2 (tin ethyl etiopurpurin)

This agent failed its pivotal Phase III trial, and Pharmacia, which had partnered with Miravant, pulled out. However,

Miravant reportedly has re-analyzed the data and plans to submit it anyway. A speaker said, "The primary endpoint at week 103 was the percent of patients losing less than 15 letters. The original analysis clearly showed a beneficial trend, but it was not statistically significant (p=.0673 vs. placebo). A per protocol population analysis is the basis of the planned NDA…Those patients who got a pre-specified minimal exposure – at least 2 treatments -- and those whose lesions at baseline were ≤3 mm showed a consistent benefit over two years vs. placebo…The visual outcome was not dependent on lesion composition…Treated patients had a statistically significant reduction in leakage at all time points. Therapy also led to marked reduction in subretinal fluid at all time points…The patients who benefited the most were those who got three treatments over six months, and a higher entry-level VA correlated with increased visual benefit." Another expert said, "This is going to die again."

NOVARTIS/QLT THERAPEUTICS' Visudyne (verteporfrin)

The company almost appears to be unaware of the competition it is likely to face soon. Visudyne continues to get tested in new patient groups.

At one session, experts debated the value of Visudyne.

Pro: Dr. Neil Bressler argued, "PDT is a vital tool…We know this is expensive, but people are willing to pay…Why bother to debate…AMD is a major and growing public health problem. Until more effective treatments are available – and we heard about many exciting ones this morning – PDT at least now, while palliative and expensive, is a vital tool."

Con: Dr. Jack Sipperley questioned the data from the (pivotal) TAP trial, the marketing of Visudyne and its cost-effectiveness.

Rheophoresis

While many doctors remain skeptical about the value of rheophoresis for AMD, the results of an unmasked, five-month randomized trial found an average of 1.6 lines of visual improvement that lasted for 12 months. A pilot, randomized, double-masked, controlled trial found 30% of patients had 3 or more lines of vision improvement at one year vs. 10% in the control group. An expert said, "I was surprised how impressive this looked in the presentation, but I also learned this only works if there are certain levels of blood lipids, and patients on a statin don't qualify. Non-statin responders might get rheophoresis, but only if they don't respond to the statin…The science is not there yet."

The MIRA-1 trial is now underway. This is a randomized, prospective, double-masked, placebo-controlled, 12-month, intent-to-treat trial of 180 patients (120 filtration, 60 control) at 12 sites. An interim analysis of the first 43 patients was "encouraging." A researcher said, "There was quick improvement after rheophoresis (1.6 lines of improvement vs. control)…and there was a decrease in the number or more atrophic appearance of drusen, with no serious treatment adverse events during the study."

Transpupillary Thermotherapy (TTT)

The randomized, prospective, sham-controlled, TTT4CNV trial of occult patients with up to 10% classic AMD started in March 2000. Enrollment was stopped early at 285 patients instead of the planned 336. An investigator said, "The DSMB feels there are no undue safety concerns, but it said we need 18- and 24-month data…5.4% of patients in the study also had concomitant glaucoma…and it was in this subgroup that we noticed an increased risk of loss of vision with TTT…When we stopped enrolling glaucoma patients, we had no problem...This is probably a dosimetry issue, which we are looking at…The TTT trial is alive and well…There are no significant safety issues with regard to treatment…and there is less than a 2% risk of visual loss."

UVEITIS

BAUSCH & LOMB'S Envision (fluocinolone acetate)

Thirty-four week results from an Envision study showed efficacy and no systemic complications. A speaker said, "It reduces recurrences…There is 3-line improvement in vision in 26% of patients…***But*** there were safety concerns in 13.5% of patients: 8.6% required filtering surgery, 3.2% hypotony, 1.4% wound leakage, 2.2% retinal detachment, 0.4% endophthalmitis…Overall, excluding cataracts the serious adverse event rate is at least 12%…We don't know the visual outcome in these patients…This is not a panacea, but it is definitely better than the present treatment for severe patients not controlled with topicals."

34-Week Results of Envision Trial

Measurement	Baseline	At 34-Weeks n=278	p-value
Mean VA (in ETDRS letters)	58.4	62.7	p=.0001
Systemic therapy	59.0%	13.7%	N/A
# of steroid injections	70.5%	2.2%	p<.0002
Topical steroid use	28.7%	8.3%	p=.0001
Use of IOP-lowering drops	34.89%	8.6%	p<.0001

BRISTOL-MYERS SQUIBB'S Kenalog (triamcinolone acetonide)

Intravitreal Kenalog is being used off-label for a variety of eye conditions, including AMD, uveitis, and macular edema. Yet, the studies have been small and endophthalmitis is a concern. A speaker said, "Thirty to fifty percent of chronic uveitis patients develop macular edema…and there is risk of permanent damage…Visual acuity gains (with Kenalog) were modest, and two patients (of 16) had several complications in

two eyes, which may limit its use in less severe eyes…More information on long-term use is still needed."

There is work being done by an unnamed company to develop a Kenalog formulation that is a single dose, non-preservative agent. An expert said, "I think that will be announced relatively soon…The preservative is the issue in Kenalog. There are patients who get pseudoendophthalmitis and some people feel that it is form the vehicle or preservative…The hope is that having a more purified form will avoid that complication."

GENERA'S squalamine

This extract from dogfish shark livers is in clinical trials for several different forms of cancer, including ovarian cancer. It also has been studied in a small number of AMD patients at a single center in Mexico by a single investigator. An expert said, "We know extremely little about it -- except that it is a monthly intravenous injection. If that is the case, that is great…but it is a long way away." Another expert said, "The data is just not believable."

MISCELLANEOUS

Heidelberg's HRA2, a high speed retinal angiography machine is selling like hotcakes. The company reportedly has more on order right now than were sold in the past nine years. An official said, "We can't make them fast enough in Germany." There are no competitors on the market and none on the near horizon for this $100,000 add-on device.

ALCON'S Patanol QD is expected to be approved in 2Q04 or 3Q04.

The annual **ASCRS survey** of its members every year, and the results this year had some interesting findings.

- Would you discontinue PDT (Visudyne) if reimbursement was cut 20%: Yes 33%, No 67%.

TTT Per Week

None	0-1	2-4	5-8
74%	18%	6%	2%

Kenalog Side Effects

Side Effect	Yes	No
Inflammation	37%	673%
Endophthalmitis	6%	94%

Kenalog Use for CNV Per week

Never	1-2	3-5	6-10	>10
55%	15%	15%	5%	9%

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