Trends-in-Medicine

July 2005
by Lynne Peterson

SUMMARY

Genentech's Lucentis appears to be a big advance in wet AMD, but it was upstaged by another Genentech drug – Avastin, another anti-VEGF agent approved to treat colorectal cancer. Avastin is available now, while Lucentis won't be FDA approved for at least another 12-18 months, and Avastin is far, far cheaper than Lucentis is expected to be. So, retinal specialists are starting to use Avastin off-label, raising questions about whether Lucentis or other new drugs in development for AMD can ever find a market. ♦ Doctors are disappointed with Macugen and many report preferring QLT/Novartis's Visudyne plus a steroid. Thus, Macugen use is expected to decrease significantly. ♦ Retinal specialists are extremely dubious about Occulogix's Rheopheresis treatment for dry AMD. The data may be sufficient for FDA approval, but convincing doctors to use it may be more difficult.

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

AMERICAN SOCIETY OF RETINA SPECIALISTS

Montreal, Canada
July 16-20, 2005

Word spread like a tsunami through the American Society of Retina Specialists (ASRS) meeting about the newly discovered benefits in wet age-related macular degeneration (AMD) from the off-label – and very inexpensive – use of a chemotherapy agent for colorectal cancer. At the beginning of the meeting, only a handful of doctors knew about intravitreal injections of Genentech's Avastin (bevacizumab), but by the end of the meeting, most doctors questioned said they plan to go home and try it.

In fact, Avastin stole the show from Genentech's Lucentis (ranibizumab), a fragment of the Avastin molecule that is being developed specifically as an intravitreal injection for AMD. The data presented on Lucentis was outstanding, but it did as much to convince doctors of the value of Avastin as to build anticipation for Lucentis. There have been no studies of Avastin, just case reports and personal experiences, but that was enough to make doctors want to use it – particularly in patients who have failed photodynamic therapy and/or Eyetech's Macugen (pegaptanib).

The excitement over Avastin is so high that it:

- May quickly kill Macugen use.
- May keep Lucentis from ever getting to market.
- Seriously clouds the outlook for other wet AMD therapies in development, including Genaera's Evizon (squalamine) and Regeneron's VEGF-TRAP.

DRUGS

GENENTECH'S Avastin (bevacizumab)

Systemic

The results of the 18-patient SANA trial – an investigator-led study of ***systemic*** Avastin (5 mg/kg) in wet AMD – were presented, and the data looked quite powerful. Patients got an infusion of Avastin at Weeks 1, 2, and 4. Overall, there was a marked improvement in visual acuity and retinal thickness at Week 1 that continued to improve out to Week 24. For instance, retinal thickness decreased 115 μm at Week 1 in the primary eye and 5 μm in the fellow eye (which decreased by 66 μm at Week 24). At 24 weeks, there was bilateral improvement in visual acuity, fluorescein angiography, ICG (indocyanine green) angiography, and OCT (optical coherence tomography).

Patients in this study were retreated if they had a loss of 5 letters associated with leakage or an increase in central retinal thickness of ≥100 μ. Researchers reported that 67% did not require retreatment through six months, and of the 33% who were retreated, four got an Avastin infusion, one an intravitreal injection of Avastin (1.25 mg) , and one Macugen.

Intravitreal

There was a groundswell of interest in off-label use of intravitreal Avastin in wet AMD. A Texas doctor said, "I'll do Avastin as soon as I get home in one patient who failed other therapies and wanted Lucentis and see how that patient does." Another said, "We're going to drop Macugen entirely and use Avastin." A third said, "I'm going home to talk to our oncologists. I'll start using Avastin as soon as I can get it."

This had Genentech officials very concerned. They were insisting they have no plans to investigate Avastin in AMD, and they were emphasizing that there are safety issues with Avastin – hypertension and cardiovascular side effects.

Experts suggested that the National Eye Institute should conduct a trial of intravitreal Avastin in AMD since Genentech won't. A Lucentis investigator tried to dampen enthusiasm for Avastin, commenting, "The (Avastin) data are interesting, but we need to see more…And results even in Phase I/II can lead to false hopes."

An AMD expert thought Dr. Philip Rosenfeld of Bascom Palmer, a Lucentis investigator and one of the first doctors to try intravitreal Avastin for AMD, was "very brave" to have tried Avastin injections, but Dr. Rosenfeld said his experience with systemic administration gave him confidence in the intravitreal route. He said he actually "sleeps better at night" after giving intravitreal Avastin than he does after systemic administration of Avastin.

A source claimed Genentech never published any animal data on Avastin in AMD and that there is no proof that Avastin doesn't work in animals, much less in humans. Another doctor wondered if Genentech deliberately didn't test Avastin in AMD in order to protect the Lucentis patent and pricing positions. Of course, Genentech officials had a different story. An official confirmed the company never actually tested Avastin in an animal model of AMD. Rather, another Genentech monoclonal antibody, Herceptin (trastuzumab), was tested for retinal permeability, but it didn't penetrate the retina sufficiently, leading the company to determine that Avastin, like Herceptin, was too large a protein to penetrate the retina. Thus, Lucentis, a fragment of Avastin, was developed after animal studies showed it did penetrate the retina.

Reportedly, toxicity studies (not sponsored by Genentech) will be started immediately after ASRS. Dr. Rosenfeld said, "There have been no true toxicity studies (of intravitreal Avastin), and now some will be going on in the next week."

Cost is likely to be a huge driver of Avastin use. A vial of Avastin reportedly costs about $500 and can treat up to 100 patients. Even with pharmacy compounding costs, the price of an Avastin injection is only $20-$30. Several retinal specialists commented that Avastin may help the subspecialty "take back their profession from the large pharmaceutical companies."

Genentech officials, asked about intravitreal Avastin, offered these comments:

- **Small numbers.** The patient in the SANA trial was a single case report. "While we understand the excitement over this (Lucentis) data, this is a rigorous development program with a lot of efficacy and safety data…One patient, a case report with intravitreal Avastin, has been put in the public domain. We think it is very premature to draw any conclusion on efficacy and safety."
- **Possible toxicity.** "We made a decision to develop an intravitreal molecule to inhibit VEGF, based on the possibility that intravitreal Avastin might have toxicity. That turned out to be a wise decision…The Lucentis molecule has a higher affinity for VEGF and no FC portion. Based on data, we thought it would have better penetration into the retina where we thought the effect would need to be." Another official said, "What we are hearing back from doctors here is that there is an unmet need, and the benefits outweigh the risks…but we believe in being very conservative."
- **No disincentives.** An official insisted the company has no strategy to disincentivize doctors from using intravitreal Avastin.

GENENTECH'S Lucentis (ranibizumab)

Lucentis is a humanized therapeutic antibody fragment (of Avastin) developed at Genentech and designed to bind and inhibit Vascular Endothelial Growth Factor A (VEGF-A), a protein that plays a critical role in angiogenesis. Genentech will market Lucentis for wet AMD in North America, and Novartis has exclusive commercialization rights for the rest of the world.

Data from three trials were presented at ASRS, and they all had the same message – Lucentis appears to be the most effective agent yet for wet AMD:

➢ **PrONTO trial.** This was a 30-patient study of OCT imaging of neovascular AMD patients treated with monthly Lucentis injections. The study found patients gained an average of 5.5 letters at Day 14 and 8.6 letters at Day 90. There also was a decrease in central retinal thickness observed as early as Day 1.

➢ **FOCUS trial.** One-year results were presented at ASRS from this 23-month, randomized, single-masked, sham-controlled Phase I/II trial of Lucentis + photodynamic therapy

(PDT) with QLT/Novartis's Visudyne (verteporfin) in 162 patients with predominantly classic subfoveal wet AMD. In the study, which was conducted at 25 sites in the U.S., an initial PDT treatment was followed by either an injection of Lucentis or a sham injection, where the doctor prepared and anesthetized the patient's eye but did not perform an injection. Retreatment was every three months at the investigator's discretion, based on the Visudyne label. A different Lucentis formulation was used in this trial from that being used in the Phase III trial. A preliminary data analysis found an increased risk of uveitis with the combination therapy, and the study protocol was amended so that Lucentis was withheld in months that PDT was administered, and this appeared to resolve the uveitis problem.

1-Year Results of the Phase I/II FOCUS Trial

Measurement	PDT alone n=56	Lucentis 0.5 mg + PDT n=105
Demographics		
Prior PDT	41.8%	45.3%
Occult with no classic	7.1%	1.9%
Minimally classic	26.8%	30.5%
Predominantly classic	66.1%	67.7%
Mean baseline VA	48.5 letters	45.1 letters
Patients with follow-up	91.1%	91.5%
Efficacy results		
Primary endpoint: Loss of <15 letters of visual acuity	67.9%	90.5% (p=.0003)
Gain of >15 letters of VA in patients ***with*** prior PDT (n=76)	3.4% (1 of 29 patients)	14.9% (7 of 47 patients)
Gain of >15 letters of VA in patients ***without*** prior PDT (n=85)	7.4% (2 of 27 patients)	31.0% (18 of 58 patients)
Secondary endpoint #1: Mean change in VA from baseline	- 8.2 letters	+ 4.9 letters
Secondary endpoint #2: Gain of >15 letters from baseline in all patients (n=161)	5.4% (3 of 56 patients)	23.8% (p=.0033) (25 of 105 patients)
Severe vision loss (≥30 letters)	8.9%	1.0% (p=.01)
Retreatment required		
At Month 6	80.4%	16.2%
At Month 9	55.4%	6.7%
At Month 12	37.5%	1.9%
Average PDT treatments	3.4	1.3
Use of PDT at 12 Months	37.5%	1.9%
Safety		
Uveitis	0	8.6%
Presumed endophthalmitis	0	4.8% 5 patients * (4 culture negative)
Hypertension	7.1%	12.4%
Key arterial thrombolic events		
Overall non-fatal events	3.6%	3.8%
MI	3.6% (2 patients)	0
Cerebrovascular accident	0	3.8% (4 patients)
Death	0	0

* Mean VA change for this group was - 4.8 letters.

There was a protocol change in FOCUS. All the patients were enrolled and had at least one round of PDT before the protocol change was made. After the change, only seven patients required PDT, for a total of eight treatments. An official commented, "Use of PDT in the combination arm is so low that it is hard to know if the amendment solved the problem."

➢ **MARINA trial.** The results were presented at ASRS from this randomized, multicenter, double-masked, sham injection-controlled Phase III trial comparing two different doses of Lucentis in 716 patients with minimally classic or occult subfoveal wet AMD. Patients were excluded who had prior subfoveal laser treatment, PDT, or another experimental treatment for wet AMD. Patients could receive PDT therapy if they converted to predominantly classic disease while on the study or if they had small, active minimally classic or occult lesions and lost ≥20 letters of visual acuity (VA) on two consecutive evaluations.

The beneficial effects of Lucentis were seen quickly and continued to increase over time, though it isn't clear whether the increase tapers off by one year. At the end of the first year, an investigator reported no difference by any subgroup examined – disc size, starting VA, minimally classic vs. occult, etc.

Retinal specialists were very impressed with the data, though there were a few criticisms, including:

- **Early data.** This is only the first year of a two-year study.
- **High placebo response.** There was a high success rate (62.2%) in the control group who received only PDT, which is higher than seen in the Visudyne TAP trial.
- **Patient selection.** Did Genentech study a more benign patient population? This is what competitors are suggesting, but they didn't produce any compelling details to prove this, so the charge was mostly dismissed.

MARINA data that have not yet been analyzed include:

- Moderate vision loss.
- Non-responders.

Other interesting points Genentech officials made about Lucentis included:

➢ **Combination with PDT.** "We know PDT creates an insult that can result in some fibrosis and scarring. It does appear that in FOCUS, if patients had prior PDT, they could still gain vision."

- **Serum measurements.** Genentech has developed an assay that can measure Lucentis levels in the blood – and it is detectable. An official said, "When it is time for a repeat dose, in the vast majority of cases, there is no detectable level in the blood."
- **New trials.** "(Avastin) does highlight the importance of continuing to develop Lucentis with Phase IIIb and Phase IV studies that will enable clinicians and patients to ask additional questions that have been posed by these studies, and where patients can get access to the drug." Officials declined to specify what specific trials will be started, but they said, "The evidence encourages us about other potential indications, and we will be looking at that. Novartis has an ongoing study in DME (diabetic macular edema)."
- **Filing strategy.** Genentech has requested fast track status from the FDA and is hoping for a decision soon. If that is accepted, the company can begin a rolling BLA submission. Genentech is not certain yet how much two-year data the FDA will require. An official said, "We will have quite a few patients in MARINA who will have completed two-year follow-up by the time of any filing. How much other two-year data from other trials we will need, we are in active discussions with the FDA about." The company also is reserving a decision on the dose for which they will seek approval until the ANCHOR trial data are available.
- **Pricing of Lucentis.** Officials would not speculate on this. Genentech was expected to price Lucentis at about $1,500 an injection, but that could be very difficult if Avastin catches on. Genentech officials were emphasizing that Lucentis would be an approved product and, therefore, reimbursable, while Avastin is off-label and probably not reimbursable. However, the difference between $30 for Avastin and $1,500 for Lucentis is so great that most doctors said patients would probably be willing to pay out-of-pocket for Avastin if they had to.
- **Arterial embolic events (ATEs).** The FOCUS and MARINA trials appear to have given the company confidence that this will not be an issue with Lucentis. "With MARINA and FOCUS, while events were observed, they are moving in different directions. At one year, it is too early to conclude anything with these small numbers, but we are encouraged there appears to be a balance in ATEs (between sham and drug)." Another official said, "The rates are what would be expected in this (elderly) population." There was no clustering of side effects at any particular time point.
- **High sham response in MARINA.** An official said, "There was some degree of PDT use in that arm. About 10% of subjects in that arm got PDT." However, he said he couldn't say yet whether the sham patients who improved were the ones who got PDT.
- **Comparison of Lucentis patients to Macugen patients.** Asked if there was any evidence that MARINA patients were earlier in their disease stage than the Macugen pivotal trial patients, an official said, "In FOCUS, half the patients had prior PDT, so the trend was not to younger lesions. In MARINA, there were no data to compare with other analyses on the age of the lesions." Another official pointed out, "In MARINA, there was statistically significant activity regardless of how we cut the data."

1-Year Results of the Phase III MARINA Trial

Measurement	PDT alone n=238	Lucentis 0.3 mg + PDT n=238	Lucentis 0.5 mg + PDT n=240	p-value (Lucentis vs. sham)
Demographics				
Follow-up	89.1%	95.0%	93.8%	---
Occult with no classic	63.4%	63.5%	61.7%	---
Minimally classic	36.6%	36.1%	37.9%	---
Predominantly classic	---	0.4%	0.4%	---
Injections (out of 12 possible)	10.8	11.5	11.3	---
Mean baseline VA	53.7 letters	53.1 letters	53.7 letters	---
Efficacy				
Primary endpoint: Loss of <15 letters of visual acuity	62.2%	94.5%	94.6%	<.0001
Secondary endpoint #1: Mean change in visual acuity from baseline	- 10.5 letters	+ 6.5 letters	+ 7.2 letters	<.0001
Secondary endpoint #2: Patients gaining ≥15 letters	4.6%	24.8%	33.8%	<.0001
Secondary endpoint #3: Patients with VA of 20/200 or worse	42.9%	12.2%	11.7%	<.0001
Patients achieving VA 20/40 or better	10.9%	38.7%	40%	<.0001
Patients losing ≥30 letters	14.3%	0.8%	1.2%	<.0001
PDT received	11%	0.4%	0.5%	---
Safety				
Uveitis	0	0.8%	0.4%	Nss
Endophthalmitis	0	0.4%*	0.8%*	Nss
Retinal tear	0	0.4%	0.4%	Nss
Vitreous hemorrhage	0	0.4%	0.4%	Nss
No inflammation	87.3%	85.7%	82.8%	Nss
Hypertension	9.7%	8.4%	8.4%	Nss
Key arterial thromboembolic events				
Overall non-fatal	0.8%	0.8%	1.7%	Nss
MI	0.4%	0.4%	0.4%	Nss
Cerebrovascular accident	0.4%	0.4%	1.3%	Nss
Death	0	0.4% (MI) **	0.8% ** †	Nss

* Culture negative ** Not related to study drug
† COPD, small bowel infarct

- **Sales force.** Officials would not provide any details on sales force plans except to say there will be more than 10 sales reps handling Lucentis.

Other Lucentis trials

Other ongoing Lucentis AMD studies include:

- **ANCHOR,** a randomized, multicenter, double-masked, active treatment controlled Phase III trial of two doses of Lucentis in 423 patients with predominantly classic wet AMD in the U.S., Europe, and Australia. Results of this study are expected in 4Q05.

- **PIER,** a randomized, multicenter, double-masked Phase IIIb trial of two doses of Lucentis vs. sham in 184 patients with wet AMD in the U.S. Lucentis is being administered once a month for the first three doses and then once every three months for two years. The results are expected in 1Q06.

- **HORIZON,** a Phase III open-label extension study, which allows eligible patients who have completed participation in certain other Lucentis clinical studies to continue to receive Lucentis.

EYETECH'S Macugen (pegaptanib)

Virtually every retinal specialist questioned expressed disappointment in the results in wet AMD with Macugen, which is administered by intravitreal injection every six weeks. Few doctors at ASRS said they are injecting it that frequently, and many sources said they are getting equal or better results with Visudyne PDT plus off-label Kenalog (Bristol-Myers Squibb, triamcinolone acetonide). A Midwest doctor said, "I don't do Macugen every six weeks for two years just because the company says I should. The guidelines from their trials are almost antiquated…I don't do follow-up tests until the third or fourth visit, then I do OCT." Despite this, the Macugen sales reps were very upbeat and positive at ASRS, saying the data on Lucentis just prove that anti-VEGF works – and they were emphasizing that they have the only anti-VEGF that is currently FDA-approved for AMD.

Yet, the outlook for Macugen is for a downward spiral in sales, with some experts predicting the company won't be around in another couple of years. While Lucentis looked like a category (anti-VEGF category) killer, it is still more than a year away from FDA approval, but the discovery of intravitreal Avastin is likely to have an immediate and dramatic impact on Macugen.

AMD

Two-year results from the two-trial, randomized, multicenter, double-masked VISION study were presented, indicating the drug continues to looks safe with two years of injections. During Year 2, 425 patients received a total of 2,663 Macugen injections. With Macugen, patients maintained or gained vision in Year 2.

2-Year Results of VISION Trial

Measurement	Macugen 0.3 mg n=128	Macugen 1.0 mg n=126	Macugen 3.0 mg n=120	Sham n=51
Number of treatments at end of 1st year	8.5			---
Number of treatments at end of 2nd year	16			---
Stable or improved vision at 52 weeks	33%			---
Stable or improved vision at 104 weeks	35%			---
Re-leakage	9% when Macugen continued 75% when Macugen stopped			---
Coronary artery disease	1%			0
Death	0.5%			0
Endophthalmitis	0			0
Retinal detachment	0.15%			N/A
Any visual loss	1.9%			N/A
Severe visual loss	0.27%			N/A
Inflammation				
Mild	5%			4%
Moderate	0			0
Severe	0			0
In fellow eye	1%			0

The drug also showed good safety. There was no evidence of cataract progression or glaucoma. A small (2-6 mm Hg) rise in IOP occurred about 30-minutes post-injection but returned to normal within a week, and mild inflammation was transient and likely due to the procedure. An investigator commented, "It should be noted that with Avastin there is a potential for systemic hypertension, proteinuria, bleeding, and thrombo-embolic events. None of this is seen with Macugen." He said Eyetech is looking actively at alternative delivery systems.

DME

The results were presented from a randomized, double-masked, dose-finding Phase II trial of Macugen in DME patients who could defer photocoagulation for 12 weeks. Macugen was injected every six weeks for 12-30 weeks (a minimum of three and a maximum of six injections). There was one case of endophthalmitis, no evidence of cataract formation or acceleration, and no increase in IOP. The lowest dose – 0.3 mg – appeared the most effective, but the trial was not powered to show statistically significant benefits by dose. However, the speaker said the trial did show Macugen:

- Improved visual acuity.
- Resorted normal macular architecture.
- Decreased the need for macular laser.
- Reduced ETDRS severity grade.
- Regressed neorevascularization.

She concluded, "The evidence seems compelling, but we need to await the results of the Phase III trial. We will start enrolling that later next month (August 2005)." She also indicated that the company will be evaluating whether a dose lower than 0.3 mg would be just as beneficial as 0.3 mg. Another expert commented, "The 0.3 mg dose could be a random variation. It could look numerically better, but the study wasn't designed to look for a statistically significant dose."

Phase II Trial of Macugen in DME

Measurement	Macugen 0.3 mg n=44	Macugen 1.0 mg n=44	Macugen 3.0 mg n=42	Sham n=42
Gain in visual acuity				
0 lines	73%	---	---	23%
1 line	59%	---	---	12%
2 lines	34%	---	---	6%
3 lines	18%	---	---	2%
Other results				
Mean change in retinal thickness	- 68 µg (p<.05)	---	---	+ 4 µg
Patients needing focal/grid laser	25% (p<.05)	30%	40%	48%
Improvement in ETDRS severity of >1 step	28%	---	---	13%

BRISTOL-MYERS SQUIBB'S Kenalog (triamcinolone acetonide)

For a brand name drug with no one actively marketing it, Kenalog sales are booming. Retinal specialists continue to find new uses for it. Safety has improved, and endophthalmitis rates have gone down with sterile techniques.

AMD

Every doctor questioned indicated intravitreal use of Kenalog (IVTA) is increasing, and many are using it in combination with PDT for wet AMD *(See Visudyne on page 7)*. A doctor from Bascom Palmer Eye Institute in Miami said, "We have already passed our 2004 usage (of IVTA), and we will be at 4,000 injections (annually) by the end of 2005."

Two key studies of IVTA are underway:

- **DRCR.net** study, sponsored by the National Eye Institute, which is evaluating outcomes of IVTA for DME.
- **SCORE** study, evaluating IVTA for venous occlusive disease.

DME

Conventional therapy is focal laser, but 26% of patients continue to lose vision despite this treatment. A speaker presented a study of 61 eyes in 54 patients who failed 1-3 sessions of focal laser and then were given an injection of 4.0 mg IVTA. The study found IVTA restored vision in 52% of patients. Although 21% of patients got increased IOP (>21 mm Hg), but all improved with either observation or topical agents.

A speaker from Brazil presented a randomized study of 36 phakic DME eyes (28 completers, 8 lost to follow-up) comparing a 40 mg sub-tenon infusion of IVTA to a 4.0 mg IVTA injection. The conclusions were that (a) both routes of administration may lead to a transitory increase in IOP and (b) IVTA injection is better than sub-tenon infusion.

A third speaker presented a retrospective chart review of 64 eyes in 38 DME patients who got a combination of laser and posterior sub-tenon IVTA. At one year, the study found that 77% had ≥2 lines of improvement, and 34% had ≥3 lines of improvement. The potential advantages of combined therapy are:

- Action of the treatments occurs by multiple pathways.
- Lower doses may be possible – lower focal laser intensity, avoiding the grid pattern, and reducing side effects.
- Potential for improved efficacy and outcomes.

Retinal vein occlusion

A small (13-patient), uncontrolled, non-randomized, retrospective study found that 100% of eyes improved at least 2 lines sometime during the follow-up period, and 9% had improvement at last follow-up. Re-injection was needed in 38% of eyes because of persistent or recurrent cystoid macular edema (CME). In 31% of patients IOP was elevated, requiring topical therapy, and ischemic conversions occurred in 31% of patients, and significant cataracts in 38% (5 of 13). The speaker said:

- 1/3 got better and stayed better.
- 1/3 got better, then worsened, were re-injected, got better again, and ultimately had their edema resolve.
- 1/3 resolved, then became ischemic.

Complications with IVTA

A study of 1,000 eyes was presented, and the researcher concluded, "It is unknown whether the newer triamcinolone preparations have a better safety profile, but Kenalog appears safe in macular disease." Other findings included:

- 1% (4 cases) developed inflammation (3 post-op CME). Of these, 80% were pseudophakic and 80% developed ocular hypertension.
- 45% of patients followed ≥12 months developed cataracts.
- 45% had IOP >21, and 20% had IOP >25, but this was typically easy to control with topical agents.
- 6 cases of sterile endophthalmitis (4 post-CME). There was no infectious endophthalmitis.

When the audience was asked how many of them use IVTA, virtually every doctor raised a hand. About 5%-10% of the doctors in the audience said they have seen a case of endophthalmitis, and about a third indicated they have seen non-sterile endophthalmitis.

QLT/NOVARTIS'S Visudyne (verteporfin)

Unlike Macugen, Visudyne is not expected to disappear. While the benefits of this photodynamic therapy for wet AMD are limited, and there is a 4% risk of severe vision loss, experts still see a role for PDT with Visudyne even with the advent of intravitreal Avastin and Lucentis. In fact, PDT with Visudyne plus IVTA has become the preferred therapy for wet AMD patients. Avastin and/or Lucentis may cut into use of this combination therapy, but it won't go away any time soon if ever.

Visudyne PDT + IVTA

Several studies were presented validating the use of this combination therapy, including:

➢ A researcher presented the results of a retrospective chart-review study of 32 patients with minimally classic subfoveal CNV with or without retinal angiomatous proliferation (RAP) lesions who received IVTA (administered ≤7 days prior to PDT or ≤30 minutes post-PDT) plus PDT. Combination retreatments were performed if there was fluorescein angiographic leakage. The conclusion was that IVTA + PDT may be effective in minimally classic CNV with or without RAP lesions.

PDT + IVTA

Measurement	All patients n=32	RAP patients n=15
Gained ≥3 lines VA	3 patients	0
Lost ≤3 lines VA or gained any VA	27 patients	13 patients
No additional treatment required	10 patients	4 patients
1 additional treatment required	10 patients	5 patients
2-6 additional treatments required	12 patients	6 patients

➢ A 199-patient study in Germany and Austria found a benefit to combination PDT + IVTA (25 mg) therapy. Nearly 60% of patients had an increase of VA, with the mean increase 1.0 line. A researcher reported, "There was a significant increase in visual acuity in all lesion types and locations." A transient increase in IOP was observed in 26.0% of patients. The IOP increase was generally controlled by topical agents, but 2.6% of patients required surgery. Side effects increased over time.

➢ A 78-patient study in Brazil found that combining PDT and IVTA reduced the need for additional treatments vs. PDT alone.

➢ A retrospective chart review of 108 patients found that profound choroidal hypoperfusion can occur following PDT + IVTA. Patients with good vision who get hypoperfusion may have severe vision loss. The hypoperfusion was most noticeable at 4-6 weeks post-treatment and faded with time. The researcher said ways are being investigated to improve the effect of combination therapy, including:

- Fluence – increased selectivity.
- Timing of laser after Visudyne infusion.
- Visudyne dose.
- Steroid dose.
- Steroid timing.
- Other combination treatments.

GENAERA'S Evizon (squalamine lactate)

Is there a future for this wet AMD agent? Sources were dubious with off-label Avastin here already and Lucentis on the horizon. Two studies were presented at ASRS, and the data looked good, but doctors noticed that the speaker only showed films of the fellow eye of patients – not the primary eyes.

➢ Preliminary safety and PK results were presented from a 3-site (all U.S.), 18-patient, open-label, multi-dose Phase II trial (Study AMD-0207) of Evizon. Three different doses were tested – a high dose (40 mg), a medium dose (20 mg), and a low dose (10 mg). In all groups, a solution of 0.25 mg/mL of Evizon was infused at a constant rate of 4 mL/minute once a week for four weeks.

Preliminary Phase II Evizon Results

Measurement	Evizon
Mean plasma concentration at Week 1	3 µg/mL
Mean plasma concentration at Week 4	8 µg/mL

The best effect in the primary eye appeared to be with the high dose, which showed a strong effect in the first five weeks, while the other two doses had a much less pronounced effect. In the fellow eyes, there was improvement with both the high and medium doses only. The 40 mg dose preserved or improved vision in all patients through four months. An investigator pointed out that one advantage to this therapy is that bilateral disease can be treated with one treatment.

There were no drug-related serious adverse events and no drug-related ophthalmic adverse events (no cataracts for IOP elevation). The most common adverse events were infusion site reactions, which were mostly mild-to-moderate. No patients withdrew due to adverse events.

The half-life of Evizon is 6-7 hours, and clearance is not dose-dependent. In the low-dose group, Evizon was detectable (>0.01 µg/mL) at 24 hours post-dose in two of the six patients.

Elimination was biphasic and did not change with repeated weekly dosing.

Interim safety and efficacy results from another study – a 46-patient, multicenter, randomized, controlled, masked Phase II trial of Evizon plus PDT – also were presented. PDT was administered at Week 3 and Evizon at Weeks 1, 2, 4, 5, and then monthly for five months. A researcher reported no drug-related serious adverse events, no drug-related ophthalmic adverse events (no cataracts and no IOP increase). Adverse events were mostly mild injection site reactions.

Evizon + PDT Phase II Results

Measurement	Evizon + PDT n=29	Placebo + PDT n=17
Predominantly classic	35%	41%
Active occult	48%	41%
Single eye AMD	21%	18%
Adverse events by ITT	63%	N/A
Moderate-to-severe adverse events	13.8%	N/A
Adverse events deemed "probably related" to study treatment	27.6%	0

ALCON'S Retaane (anecortave)

Sources indicated this product is still at least two years away from FDA approval for wet AMD – if new juxtascleral injection delivery techniques avoid leakage and improve the efficacy enough to result in a new and positive clinical trial. A talk that was supposed to be a review of clinical trials in AMD was one of the few times at the meeting that Retaane even came up. The speaker suggested several things that could have played a part in the failure of the pivotal Retaane trial, including:

- **An excess of small lesions.**
- **Faster treatment.** Median time to treatment from onset of symptoms was 37 days compared to 270 days in previous trials.
- **More aggressive lesions.**

CASE STUDIES

A panel of AMD experts reviewed nine cases. Their treatment choices did not reflect the excitement over Avastin, and some of their comments – and audience responses – during this session were particularly interesting, including:

1. ***An 85-year-old man with new confirmed, new onset AMD, and VA 20/25:*** The panel agreed they would simply observe this patient for a while.

2. ***A 76-year-old woman with problems for 3 months, slowly deteriorating vision, and VA 20/50:*** The panel would probably give Macugen (not Avastin since this was first-line therapy, an expert pointed out), but PDT would also be appropriate.

3. ***A 79-year-old with VA 20/50 and a suspicion of disease progression under the foveal center:*** Three panel members would give PDT alone, and two would give PDT + IVTA. No one would give Macugen.

4. ***A 68-year-old woman with VA 20/400 and decrease in vision for 4 months:*** Most panel members said they would give PDT alone, but about two-thirds of the audience would give PDT + IVTA and the other third would give PDT alone. Dr. Neil Bressler of the Wilmer Eye Institute pointed out, "We need to know in the future how PDT + IVTA compares to Lucentis. Efficacy comes first." Dr. Rosenfeld said, "I routinely treated with (PDT plus) Kenalog…but glaucoma is catching up with that therapy, so I'm becoming less enamored with the combination therapy…An interesting trial but one I don't think is likely to be done would be Lucentis vs. PDT + IVTA." Another expert said, "Given the stunning results (with Lucentis) yesterday, that is a non-starter."

5. ***A 79-year-old man with distortion for 2 weeks and VA 20/40:*** The panel was divided on how they would treat this patient – two would use PDT alone, two would use PDT + IVTA, and two would use Macugen alone.

6. ***A 90-year-old woman who in one month has dropped to 20/80 in one eye:*** Everyone on the panel would use Macugen, but only about two-thirds of the audience would use Macugen. The other third of the audience would use PDT + IVTA.

7. ***A 94-year-old woman with 20/400 VA OS and a RAP lesion:*** Again, the panel was divided on how to treat this patient. Some panel members were concerned that additional treatments would not be helpful; others thought Macugen would be worth a try, and one opted for PDT + IVTA.

8. ***A 66-year-old man with worsening vision OS for three months, VA 20/40, and peripapillary lesions starting to bleed:*** Panel members generally thought a laser would be the best option.

9. ***An 81-year-old woman with VA 20/40, a monster lesion, and bleeding in the better eye:*** The treatment of choice was Macugen.

DEVICES

Visualization

A study of 100 consecutive, newly-diagnosed wet AMD patients found a role for all three of the imaging modalities currently in use:

- **Fluorescein angiography** (FA) for confirming CNV. In these patients, FA found 15% were predominantly classic, 15% minimally classic, and 70% occult.
- **ICG** for determining the size, location, and composition of the lesion, particularly when blood and PED (pigment epithelial detachment) are present. With ICG, RAP and PCV (polypoidal choroidal vasculopathy) patients were identified – 2% RAP and 7% PCV in the minimally classic, and 17% RAP and 19% PCV in the occult. The speaker said, "With ICG, we were better able to stratify the neovascularization of PED, RAP, and PCV, and the natural course and treatment are different for the lesions."
- **OCT** for determining the state of the retina.

Subretinal radiation

A pilot trial of 10 patients found that subretinal radiation for occult AMD resulted in no visual improvement and was not safe. Adverse events were frequent, with moderate visual loss in 50%-80% of patients, RPE (retinal pigment epithelium) tears in 80%, and subretinal hemorrhage in 50%.

ALLERGAN'S Posurdex

Posurdex is a very small, biodegradable, sustained-release implant for delivering drugs to the back of the eye (a drug delivery system). The initial testing has been with dexamethasone. Posurdex currently is in Phase III development.

At ASRS, a speaker presented a study in human retinal pigment epithelial cells (ARPE19) and rat neurosensory cells (R-28) that found dexamethasone – at a concentration up to at least five times that clinically used – is not toxic and may be a reasonable alternative to IVTA. It had no effect on cell viability except at the highest dose (1 mg/mL), and that effect appeared to be due to the benzyl alcohol component.

Potency of Steroids

Steroid	Anti-inflammatory potency
Betamethasone	20-30
Dexamethasone	20-30
Prednisolone	4
Triamcinolone	4
Hydrocortisone	1

However, the short half-life of dexamethasone means that an extended release delivery system may be required for clinical utility. The investigator said, "We are looking at Posurdex now."

BAUSCH & LOMB'S Retisert

Retisert is an intravitreal device that is inserted into the back of the eye and delivers time-release fluocinolone acetonide. The FDA granted orphan drug approval in April 2005 for the treatment of chronic, non-infectious uveitis affecting the posterior segment of the eye.

One of the key problems with Retisert is the price – $18,000. A B&L official said the company is aiming for 1,000 implants this year due to pent up demand, and then about 500 next year. He suggested that most usage will be by the 20-25 uveitis specialists in the country.

Retinal specialists believe Retisert has a role, but for a very small segment of patients. Most sources estimated that they would have only one patient a year who might be a candidate, but a California doctor said he probably had five or six candidates, though he wasn't sure how many would be interested.

Reimbursement also is an issue. A company official noted, "Hospitals won't allow use of Retisert unless it is reimbursed. We have an outside firm handling pre-approvals. Medicare has paid for at least two in California so far."

DUTCH OPHTHALMICS' Vince (vitreoretinal internal limiting membrane color enhancer)

Gastroenterologists stain gastrointestinal tissues to visualize tumors and inflammations. Retinal surgeons were introduced to a new term for them – chromovitrectomy (staining during vitreoretinal surgery).

OCCULOGIX'S Rheopheresis

Rheopheresis is approved for high-risk dry AMD patients in Canada and Europe, and it is being reimbursed in Germany but not in Canada. U.S. doctors are very dubious about it, and all those questioned said they would not be convinced even if the pivotal MIRA-1 trial meets its primary endpoint. They pointed out that MIRA-1 is a small (150-patient) trial and the requirements for FDA approval of this device are lower than for a drug. Several also commented that FDA approval wouldn't necessarily mean they would use Rheopheresis or that CMS would reimburse for it.

Yet, company officials are very upbeat and optimistic about the MIRA-1 trial, FDA approval, and market uptake. Seven U.S. retinal specialists and one Canadian doctor are investigators in the MIRA-1 trial, and Occulogix is recruiting doctors for a Scientific Advisory Board.

Rheopheresis is a double-filtration plasma pheresis therapy for dry AMD that purportedly eliminates high-molecular weight proteins, including fibrinogen, a2-macroglobulin, LDL, fibronectin, von Willebrand factor, and perhaps multimeric vitornectic. It also reduces blood and plasma viscosity. It is

an outpatient therapy that takes about three hours to perform. The thought is that AMD is, at least in part, a microcirculatory disorder of the retina.

An official said the pivotal Phase III MIRA-1 trial completed enrollment in December 2004, and treatments were all completed in February 2005. The 12-month follow-up will be completed in December 2005, and the results may be presented in 1Q06 at one of these meetings:

- A macula meeting January 13, 2006, in New York City.
- **Royal Hawaiian Eye,** January 15, 2006, Honolulu.
- **Macula Society,** February 22-25, 2006 in Carlsbad, CA.

MIRA-1 is a randomized, prospective, placebo-controlled, double-masked trial comparing Rheopheresis and sham (placebo) in 150 patients with late-stage, high-risk, dry AMD and elevated plasma levels of hemorheologic macromolecules. The primary endpoint is mean line change in log MAR best corrected visual acuity (by ETDRS evaluation) in the primary eye. Secondary endpoints include comparison of BCVA in the fellow eye and scores on the PVSRT and the 25-item version of the Visual Function Questionnaire of the NEI. The interim results of MIRA-1 were published in the ***Canadian Journal of Ophthalmology*** earlier this year.

MIRA-1 Interim Efficacy Results (n=43)

Measurement	Rheopheresis	Placebo
Loss of <2 lines of BCVA in all primary eyes		
3 months	0	6.7%
6 months	0	7.7%
9 months	4.3%	15.4%
12 months	8%	18.2%
Loss of <2 lines of BCVA in primary eyes with baseline BCVA <20/40		
3 months	0	11.1%
6 months	0	14.3%
9 months	6.3%	25.0%
12 months	5.3%	28.6%
Increase in BCVA		
≥2 lines	28%	18%
≥3 lines	12%	0

RheoNet Registry

Measurement	% of all patients	% of AMD patients
Total adverse events	5.35%	5.41%
Discontinuations for adverse events	1.84%	0.51%
Transient hypertension	6.91%	6.54%
Hypertension prevented complete treatment	1.0%	0.86%
Mean number of treatments	8.7	---
Mean change from baseline in VA by ETDRS	Up 0.9 lines	Up 0.3 lines

At ASRS, researchers presented an analysis of the safety and efficacy of Rheopheresis in the RheoNet Registry. So far, 4,776 Rheopheresis treatments have been administered to 717 patients, including 508 AMD patients. The conclusion was that Rheopheresis is a safe therapy for elderly patients with dry AMD. Vision in AMD patients remained about the same as in the MIRA interim report, with 89% of patients having stable vision.

SYNERGETICS' Photon

A speaker reviewed the advantages of various light colors, and the edge went to yellow light. The advantage of yellow light is greater safety – which means the power can be increased with safety still remaining higher than the current gold standard. A Florida doctor said the presentation was enough to tip the scales in his choice between Synergetics' Photon and Alcon's Accurus.

Accurus was described as a "true white" light but with some blue light that compromises its safety. Most of the audience raised their hand when asked if they would operate with a yellow light that is 10 times safer than the current gold standard. A speaker said, "My thought is that greater power is inducing a fundamental change in how we all operate…We may operate with lights on in the room…I use Photon with a lot of power, and particularly with peripheral viewing devices."

Color	Efficacy	Safety
Magenta	Poor	Poor
Cyan	Good luminescence	Poor
Green	Moderate	5x current gold standard
Yellow	Good	10x current gold standard

TRANSPUPILLARY THERMOTHERAPY (TTT) FOR DRY AMD

The results of the failed TTT4CNV trial were reviewed. While this trial did not show a statistical benefit to TTT, a subgroup analysis of eyes with poorer baseline VA indicated a treatment benefit. However, doctors interviewed at ASRS said they have mainly abandoned TTT.

VISIONCARE OPHTHALMIC TECHNOLOGIES' Implantable Miniature Telescope (IMT)

This privately held company has developed a device that provides AMD patients with a 60% field of vision as opposed to only 20% with an external telescope. VisionCare expects to file before the end of 2005 and is hoping for approval in March/April 2006. This is an air-filled device, but an investigator said patients can still fly in an airplane with the device.

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 were: (a) the difficulty of examining the retina through the implant, (b) how to treat new bleeds, and (3) retinal detachments.

At ASRS, one-year results from a Phase II/III trial were presented, and at least one of those concerns appear to have been answered. There were no retinal detachments. In this study, 206 of 217 planned procedures were completed (11 aborted), and the implant was removed in three eyes (two due to condensation in the implant, and one at the patient's request). The primary VA endpoint was met in 90% of patients, vs. the 50% target. An investigator said, "The challenge is patient selection and picking the correct eye when the patient has a problem in both eyes…Patients who got a device more often than not used the implant for task-specific work like painting."

Phase II/III Results with IMT002

Measurement	IMT002 n=192
VA improvement ≥3 lines	67%
BCNVA or BCDVA ≥2 lines	89%
Distant VA ≥2 lines	80%
Near VA ≥2 lines	83%
Overall improvement in quality of life score	Up 7 points
Increase in quality of life subscores (task-specific and psychosocial)	8-14 point increase
Safety	
Serious adverse events	1 recurrent CNV successfully treated with argon laser
Corneal decompensation	None
Retinal detachments	None

THE HEALTH OF THE SUBSPECIALTY

Dr. William Rich III, Director of Health Policy for the American Academy of Ophthalmology (AAO) warned retinal specialists that the threats to their Medicare fee schedule comes from:

- Explosion of drugs, some with marginal evidence of efficacy.
- Tremendous growth in non-evidence-based diagnostic testing services.
- Politically-motivated limitations on beneficiary risk.
- Move away from a limited healthcare program.

Dr. Rich said the political influence of industry precludes any rational application of an evidence-based approach to health care, and he argued that the evaluation of new technology and the clinical application of new drugs is best done by involved physicians – but he noted that physicians and professional societies are not an important player in the evaluation of new modalities of care "unless they are invited to the table by industry." The future, he noted means "a tightening pool of money," predicting the demands of evidence-based medicine will lead to a changed role for specialty societies, "The AAO and subspecialties will no longer advocate the payment of every drug and device on the market – or value-blind cuts in reimbursement are inevitable."

♦