Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Sources remain dubious about the outlook for **Bausch & Lomb**'s back-of-the-eye steroid implant, Envision. **Bristol-Myers Squibb**'s Kenalog was the hottest topic at the 2002 Retina Congress, and it's being used to treat almost everything – posterior uveitis, AMD, DME, and more. Doctors are disappointed with **Novartis/QLT**'s Visudyne, and many are doing TTT off-label for AMD, but doctors are split on its safety and effectiveness. The new product that got the most positive reception was **Genentech's** VEGF, rhuFAB-V2. The 12-month data on **Alcon**'s anecortave was well-received, but there was little critical or in-depth discussion, and most doctors did not even realize that there were significant dropouts in the trial.

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2002 RETINA CONGRESS
San Francisco, CA
September 29 – October 2, 2002

This was a joint meeting of the Retina Society and the Vitreous Society. The Vitreous Society voted at the meeting to change its name to the American Society of Retina Specialists. Following is a report on selected topics from this meeting.

BAUSCH & LOMB's Envision
(fluocinolone acetate)

Envision was barely mentioned except for one short data presentation, buried in the middle of several studies on Kenalog. Even a B&L official described the presentation as poor.

Among the concerns about Envision expressed by doctors at the meeting:

- **Cost**, especially with the growing popularity of Kenalog injections (See Kenalog below).
- **Cataract formation**. An expert said, "The cataracts are a concern, and I'd like to know how those patients do after cataract surgery." However, a B&L official said patients have had cataract operations post-Envision, and have done fine.
- **FDA approval**. An expert said, "The efficacy data is okay, but it doesn't knock your socks off. The 0.5 mg dose doesn't work as well as the 2.0 mg dose. It's safer, but it doesn't have as good an effect." He thought the FDA "might" approve Envision on six-month data, but he said he wouldn't expect much use by retinal surgeons until and unless there is three year data – and he warned that the FDA may not approve it without three year data. A B&L official said the company realizes that it may be a long-shot to get FDA approval for a three-year implant on six-month data, but he said the company thought it was "worth a try." He explained, "You can't get approval based on changes in visual acuity without three-year data, and we're not sure we can get FDA approval on six-month retinal thickening data, but we are trying. We don't expect much use with just six-month data – I wouldn't use it myself."

In the discussion at the end of the session where the Envision data was presented, several questions were posed by the audience and answered by a researcher that are interesting, including:

- *Why do intravitreal implants instead of a sub-tenon approach?* "Sub-tenon takes three weeks to work, and not all patients respond. The intravitreal implant works in one week, and most patients respond."
- *What is the status of the diabetic macular edema trial?* "The NIH Eye Institute will set up a DME consortium to answer this question with controlled trials."

Data on B&L's 180-patient DME trial will be ready in 1Q03 and may be presented at ARVO 2003.

BRISTOL-MYERS SQUIBB's Kenalog
(triamcinolone acetonide)

This meeting was a love fest for Kenalog, which was probably the hottest topic at the meeting. More papers were submitted about Kenalog than anything else. Most retinal surgeons appear to be using this injectable steroid off-label to treat a variety of eye diseases -- everything from AMD to DME, posterior uveitis and more -- and with good success. Numerous small trials of Kenalog were presented that were more anecdotal experiences than rigorous trials, and all but one showed positive results.

ALCON's Anecortave acetate

Alcon presented 12 month Phase II data from the C-98-03 trial. This is an ongoing, 24-month, double-masked, randomized, monotherapy study with re-injection every six months. The six-month data was presented at ARVO in April 2002. A two-year Phase III trial of 522 patients comparing anecortave (15 mg) to PDT with Visudyne is just beginning, with the first analysis at 12 months (probably early to mid-2004).

As a reminder: There were 128 patients (79% with predominantly classic AMD and 21% with "mostly classic" AMD) at 18 sites in this study. There are four arms: 30 mg (n=33); 15 mg (n=33), 3 mg (n=32) and placebo (n=30). The study objective was the retrobulbar depot effect on visual acuity changes and CNV lesion growth. The trials have not shown a dose-response curve, and the company has chosen the 15 mg dose for further development.

The questions raised about the anecortave trials at ARVO remain, but doctors at this meeting were not very concerned about any of them. However, when asked about these findings, several medical researchers from other specialties agreed that the data is "uninterpretable" with such a high drop out rate, and one warned that the drop-outs raise the question of bias in the results. The overhanging issues include:

- **Small numbers.** The number of patients in the trial, and in each arm, were small to start with and significantly smaller in the final analysis.
- **Side effects.** This drug was praised for its safety – no cataracts, no increase in IOP -- but the "abnormal vision" side effect still has not been explained or elaborated upon.
- **Lack of dose-response.** An explanation suggested for this was that the 30 mg dose may congeal in the eye into a spherical shape, providing less contact with the scleral surface than the 15 mg dose does.
- **Drop-outs.** Altogether, 52 of the 128 patients dropped out of the study before the 12-month mark, a 41% dropout rate, and the majority dropped out after the six-month time point. Sixteen of the 33 patients in the 15 mg arm dropped out, but a researcher said that only three of these dropped out due to disease progression. Half of the 30 placebo patients dropped out.
- Dropouts were not mentioned in the oral data presentation, and no one in the audience asked about it. The drop out rate in the 15 mg arm was 40%, and it was 52% in the placebo arm. The company said it used a "last observation carried forward" approach that gave the results reported, but sources questioned whether that is an appropriate way to record responders.

An alternative analysis of this data might be: In the 15 mg anecortave arm 79% of 33 patients would be 26 responders, but not that many completed the trial. 79% of 17 patients is 13 responders, and 13/33 gives a response rate of 39%. It is doubtful that this difference from placebo is statistically significant.

< 3 lines Vision Loss in C-98-03 Trial

15 mg anecortave		Placebo	
n=33	79%	n=30	53%
n=17	~39%	n=15	27%

Results of C-98-03 Anecortave Monotherapy Trial

Endpoint	12-month Results		6-month Results			
	15 mg anecortave	Placebo	30 mg anecortave	15 mg anecortave	3 mg anecortave	Placebo
<3 lines vision loss	79%*	53%	75%	88%	75%	70%
Predominantly classic AMD	84%*	50%	N/A	N/A	N/A	N/A
≥2 lines vision improvement	9%	3%	18%	N/A	6%	0%
Predominantly classic AMD	12%	0%	N/A.	N/A.	N/A.	N/A.
≥6 lines vision loss	0%*	23%	N/A.	N/A.	N/A.	N/A.

*p<.05

GENENTECH'S rhuFAB-V2

If there was excitement about any new drug for retina disorders, it is this. Speakers mentioned it, doctors talked about it, and the company had a good presence at the meeting. Genentech may not be as well known in the retina world as Alcon, and it doesn't have the ophthalmology marketing power of Alcon, but it is getting its name out. Phase I/II data on rhuFAB in 60 AMD patients was encouraging. Two dosing regimens were tested:

a. 0.3 mg every 4 weeks times 3 (4 injections)
b. an initial dose of 0.3 mg and then 0.5 mg every 4 weeks times 3 (4 injections)

RhuFAB-V2 Phase I/II Results

Vision Loss £ 3 lines	Control n=11	RhuFAB 300 mg n=25	RhuFAB 500 mg n=28
Visual acuity at day 98	-4.9	+8.8	+9.1
Loss of 15 letters	20%	8%	4%
No change or and increase of ≤ 15 letters	80%	92%	96%
Increase of ≥ 15 letters	0	32%	21%
≥3 line gain	0	32%	21%
2 line gain	30%	68%	64%
Any gain	30%	80%	86%
Change in leakage	-.02	-2.44	-1.59
Subretinal leakage	.54	-2.63	-.7

The most common side effect was transient inflammation, mostly after the first injection, but there were two serious adverse events – once case of endophthalmitis and one case or recurrent uveitis. No new antibodies were detected. A researcher said, "The majority of the visual acuity) gain was early – by Day 14 – and then it was maintained over time...This drug has two effects: (1) a profound anti-permeability effect, and (2) the membrane actually shrinks in size by one-third to one-half. " A doctor in the audience commented, "One case of endophthalmitis in 52 patients is unacceptable."

Dotors in the audience had several intersting questions for the presenter, incuding:

Question: *Why there was less efficacy in some patients with the higher dose?*
Answer: A rhuFAB researcher said, "The numbers were too small to tell differences between the dosages. We will follow that over time."

Question: *Which method of analysis do you prefer – fluorescein angiography or OCT?*
Answer: Ten of these patients were studied by OCT, and researchers reported they found that, over time, retinal thickness decreased – and the thinner the retina, the better the visual acuity. A rhuFAB researcher concluded: "OCT is very useful for these patients."

Question: *What do you think of combining this with PDT?*
Answer: A doctor in the audience said, "1`We studied FAB and PDT in monkeys, with weekly intravitreal injections and found the combination had no leakage."

NOVARTIS/QLT THERAPEUTICS' Visudyne
(verteporfrin)

The audience at a workshop offered some insight into Visudyne practice patterns and attitudes:

- A speaker commented that he usually only gives a patient two Visudyne treatments.
- Very few doctors thought Visudyne stabilized vision, and the speaker agreed with them. He said, "PDT slows progression in most patients, but it doesn't stabilize vision."
- CMS does not pay for Visudyne on occult patients.
- The size of the lesion does matter, especially in occult lesions (where smaller is better).
- Infusion-related pain occurs in 2.2%-9.6% of patients and can be in a variety of locations including the back, chest, leg, etc.
- There are no real safety concerns with Visudyne.
- Most doctors do not re-treat unless there is leakage; they don't do it simply on a time basis.

Visudyne Results at 24 Months

Vision Loss £ 3 lines	PDT	Placebo
Predominantly classic AMD	44%	68%
Pure occult AMD	24%	50%

** Source: Physician lecture*

TRANSPUPILLARY THERMOTHERAPY (TTT)

About half the doctors questioned already are doing TTT off-label. The other half either have had problems with it, don't believe it works, or have heard of other doctors with bad results. So, the members were pretty evenly split on this issue, and the multicenter U.S. trial that is ongoing may finally settle this debate when that data becomes available. A New York doctor said, "We looked retrospectively at 370 eyes treated with TTT and found 1.6% (6 patients) had visual complications related to treatment." Another doctor said, "The adverse events are comparable to other treatments." A third said, "We've seen some pseudoendophthalmitis, but it resolved on its own."

A Canadian study comparing TTT and Visudyne was halted when Visudyne was approved, but results on the 125 patients treated were presented. A researcher said, "The data might

suggest there is more visual acuity loss with PDT but that final visual acuity is better with PDT, but you can't compare them that way because of the different baselines."

Average readings	PDT n=68	TTT n=57	p-value
Number of treatments	2.13	1.65	nss
Visual acuity	1.13	1.35	N/A
Vision pre-treatment	.53	.86	p=.001
Vision post treatment	.95	1.09	nss
Change in vision	-.42	-.26	nss

MISCELLANEOUS

OPTICAL COHERENCE TOMOGRAPHY (OCT)

Optical coherence tomography is a diagnostic procedure in which a scanning light is used to create a digital cross-section image of the retina. The scanning light is aimed at the retina, and a computer senses the amount of light reflected by the retina to create the cross-section image. This diagnostic test is a tool for diagnosing glaucoma, detecting macular holes, catch early hints of diabetic retinopathy. Retina specialists are very interested in this technology, and it is gaining popularity.

Blue Cross/Blue Shield is not reimbursing for OCT tests, based on an assessment by its Technology Evaluation Center (TEC), but the Retina Society is trying to get that decision reversed. Many other carriers have been reimbursing for it, and doctors are convinced that they will continue to pay for it. A researcher commented, "I believe OCT will be a useful tool for analyzing AMD treatment drugs."

Two of the companies that make these instruments and their products are: Laser Diagnostic Technologies' GDx Nerve Fiber Analyzer and Heidelberg's Optical Coherence Tomography.

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AKORN'S Indocyanine Green (ICG).

Despite Akorn's de-listing from the NASDAQ in June 2002, the use of ICG imaging to help in the diagnosis of retinopathies is gaining popularity. One study pointed to the value of ICG in PDT for central serous chorioretinopathy.

The results were presented from a survey of 300 retina surgeons conducted just prior to the meeting:

- 79% of doctors doing PDT said they were doing it in their office.
- More than half had one or more bottles of wasted Visudyne in the past year.
- Those not doing PDT said the main reasons were:
  - startup cost (25%)
  - profit margin too low (14%)
  - unconvincing data (19%)
  - stopped for poor results (14%)
  - other (29%)
- Most doctors do not consider PDT cost-effective.
- Less than half the doctors (45) do ICG evaluation of new patients with signs of wet AMD, but among those who do use it, ICG is done from 15%-25% of the time. ICG is only occasionally useful for treatment decisions.
- Only 18% of doctors are currently getting reimbursed for TTT for AMD.

TTT Performed Per Week

None	0-1	2-4	5-8
70%	21%	7%	1%

Cost-effectiveness of PDT (Visudyne)

Not	Barely	Moderately	Very
34%	45%	18%	4%

Wasted Visudyne Bottles in the last 12 Months

None	1	2-5	6-10	>10
29%	16%	40%	7%	9%

Satisfaction with Visudyne

	Unsatisfied	Minimally satisfied	Moderately satisfied	Very satisfied
Patients	8%	42%	46%	4%
Doctors	10%	38%	46%	5%

Kenalog Cases Done Weekly

	None	1-2	3-5	6-10	>10
For DME	48%	16%	14%	7%	15%
For CNV	80%	9%	4%	2%	5%

Preferred Brand of Laser

Brand	Hospital	Office Procedure
Iridex	34%	16%
Lumenis	39%	63%
Nidek	2%	2%
HGM	18%	9%
Other	7%	10%