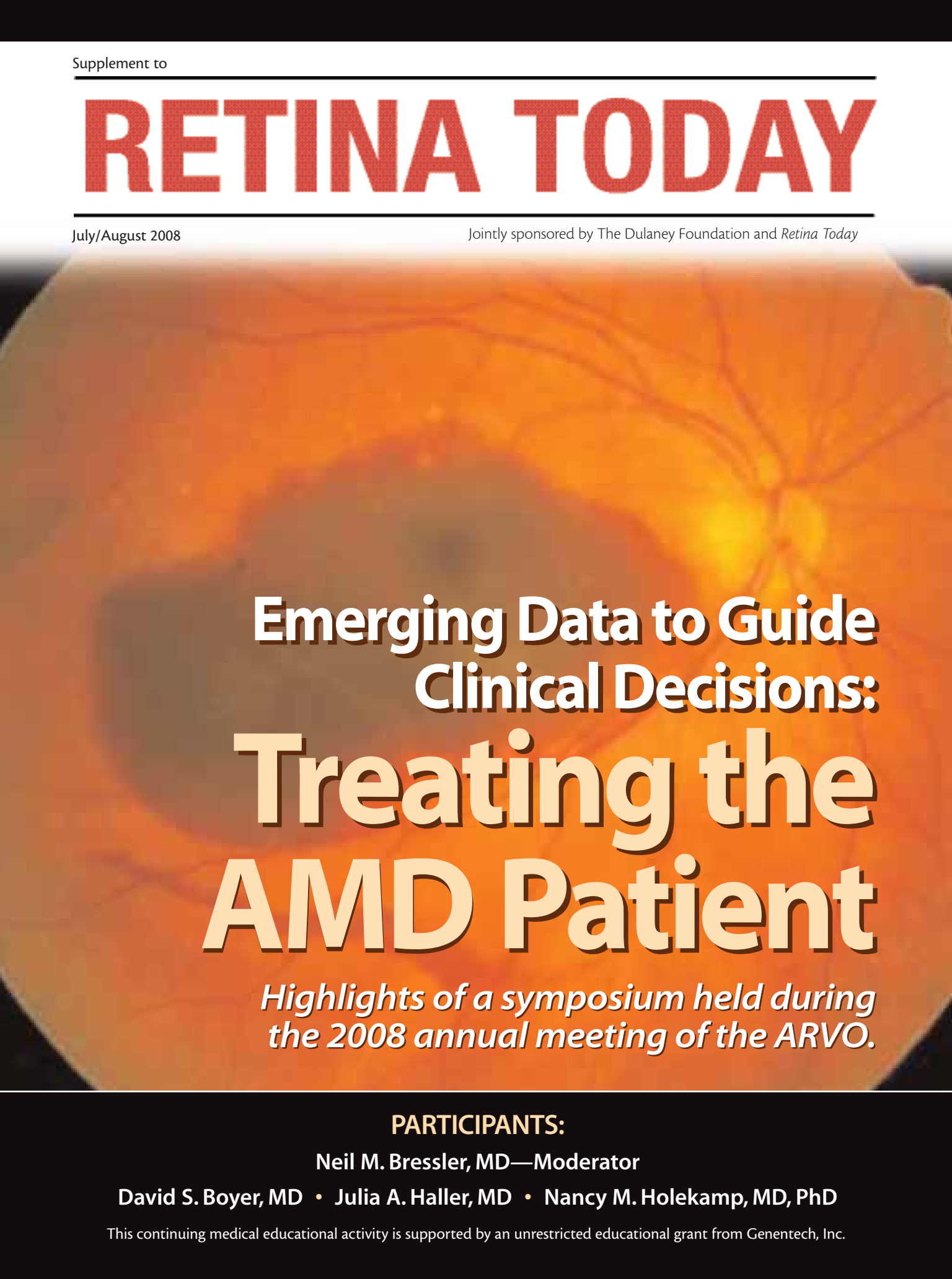


Supplement to

RETINA TODAY

July/August 2008

Jointly sponsored by The Dulaney Foundation and *Retina Today*



Emerging Data to Guide Clinical Decisions: Treating the AMD Patient

*Highlights of a symposium held during
the 2008 annual meeting of the ARVO.*

PARTICIPANTS:

Neil M. Bressler, MD—Moderator

David S. Boyer, MD • Julia A. Haller, MD • Nancy M. Holekamp, MD, PhD

This continuing medical educational activity is supported by an unrestricted educational grant from Genentech, Inc.

Emerging Data to Guide Clinical Decisions: Treating the AMD Patient

Highlights of a symposium held during the 2008 annual meeting of the ARVO.

Jointly sponsored by The Dulaney Foundation and *Retina Today*.

Release date: July 2008. Expiration date: July 2009.

This continuing medical education activity is supported by an unrestricted educational grant from Genentech Inc.

STATEMENT OF NEED

The development of vascular endothelial growth factor (VEGF) inhibitors for treating neovascular age-related macular degeneration (AMD) has drastically changed the practice patterns of retina specialists. The visual acuity gains that have been documented with the use of ranibizumab are particularly exciting, but questions remain, including those associated with safety, cost, and frequency of dosing. Several studies, many that are still under way, evaluate various combinations of drugs to extend and maximize the effects of ranibizumab,^{1,2} as well as methods that include imaging technologies to gauge the best retreatment patterns.

A better understanding of this disease state and current and future management options is critical for practitioners to effectively treat patients who suffer from AMD.

1. Rosenfeld PJ, Fung AE, Lalwani GA, Michels S, Venkatraman AS, Puliafito CA. Visual acuity outcomes following a variable-dosing regimen for ranibizumab (Lucentis) in neovascular AMD: the PrONTO Study. Presented at: The ARVO; April 30-May 4, 2006; Fort Lauderdale, FL. Abstract 2958.

2. Spaide R. Ranibizumab according to need: a treatment for age-related macular degeneration. *Am J Ophthalmol*. 2007;143:679-680.

TARGET AUDIENCE

This activity is designed for retina specialists and other ophthalmologists.

LEARNING OBJECTIVES

Upon successfully completing this learning program, participants should be able to:

- Analyze the latest data on the epidemiology, impact, and underlying pathophysiology of AMD
- Evaluate the efficacy, appropriate use, and safety profiles of currently available therapies for AMD
- Apply clinical trial data to therapeutic decisions in patients with AMD
- Identify emerging therapeutic strategies and assess their potential clinical value.

METHOD OF INSTRUCTION

Participants should read the continuing medical education (CME) activity in its entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit <http://www.dulaneyfoundation.org> and click "Online Courses."

Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may

print out a CME credit letter awarding 1 AMA PRA Category 1 Credit.™ The estimated time to complete this activity is 1 hour.

ACCREDITATION/DESIGNATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and *Retina Today*. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, anyone in a position to affect the content of a CME activity is required to disclose to the activity participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE DECLARATION

Neil M. Bressler, MD, discloses that grants to investigators at The Johns Hopkins University are negotiated and administered by the institution, which receives the grants, typically through the Office of Research Administration. Individual investigators who participate in the sponsored project(s) are not directly compensated by the sponsor, but may receive salary or other support from the institution to support their effort on the project(s).

Dr. Bressler is principal Investigator for: Acucela, Allergan Inc., Apeliotus Technologies, AstraZeneca, Athenagen, Bausch & Lomb, Carl Zeiss Meditec, Fovea, Genentech Inc., Jerini, Notal Vision, Novartis Ophthalmics, OSI/Eyetech, Othera, QLT, Regeneron, and TargeGen. He is a consultant for AstraZeneca, Genentech, Notal Vision, and Pfizer.

David S. Boyer, MD, has received grant/research support from Alcon, Allergan, Genentech and Novartis. He is a consultant and speaker for Alcon, Genentech, Novartis, and Pfizer.

Julia A. Haller, MD, has served as an advisor or consultant to Acuity, Allergan, Bausch & Lomb, Genentech, MacuSight, Neurotech, Novartis, and OptiMedica.

Nancy M. Holekamp, MD, is a consultant for Alcon and Genentech. She is a speaker for Genentech.

All those involved in the planning, editing, and peer review of this educational activity have indicated they have no financial relationships to disclose.

FACULTY CREDENTIALS

Neil M. Bressler, MD, is James P. Gills Professor of Ophthalmology, The Wilmer Eye Institute, Johns Hopkins University in Baltimore. Participation by Dr. Bressler in this activity does not constitute or imply endorsement by the Johns Hopkins University, the Johns Hopkins Hospital or the Johns Hopkins Health System.

David Boyer, MD, is a partner with Retinal-Vitreous Associates Medical Group in Los Angeles.

Julia A. Haller, MD, is Ophthalmologist-in-Chief, Wills Eye Institute, Professor and Chair, Department of Ophthalmology, Jefferson Medical College of Thomas Jefferson University in Philadelphia.

Nancy Holekamp, MD, is Associate Clinical Professor, Ophthalmology and Visual Sciences, Washington University School of Medicine in St. Louis, and partner, Barnes Retina Institute in St. Louis. ■

TABLE OF CONTENTS

4 Vision-related Function After Ranibizumab Treatment

By Neil M. Bressler, MD

6 Applying Clinical Trial Data in Daily Practice

By David S. Boyer, MD

10 Implementing Intravitreal Injections in Clinical Practice

By Nancy Holekamp, MD

11 Ethical Considerations

By Nancy Holekamp, MD

13 Persistent Challenges in AMD Management

By Julia A. Haller, MD

Vision-related Function After Ranibizumab Treatment

24-month results from the ANCHOR and MARINA trials.

BY NEIL M. BRESSLER, MD



Investigators from the various clinical trials for age-related macular degeneration (AMD) report visual acuity measurements derived from counting letters on an eye chart. As ophthalmologists, we translate that information and say that it probably reflects how the person functions. These letter scores do not necessarily correspond to visual function, however, because different types of ocular damage can cause similar changes on an eye chart. A patient with a homonymous hemianopia, for example, could have the same letter score as a patient with a scotoma from geographic atrophy.

We must remember that vision is not only about reading. It is recognizing people's faces—entering a room confident that you will know whom you are meeting—and other activities that are not so easily measured.

The ANCHOR trial, which looked at predominantly classic lesions, compared the visual acuity outcome of monthly ranibizumab (Lucentis, Genentech Inc.) therapy with that achieved with photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics) as often as every 3 months. As you know, the ANCHOR trial proved that ranibizumab was superior to PDT, which we already knew was superior to no treatment.¹

In addition, the ranibizumab-treated patients, on average, had greater improvements in their self-reported quality-of-life outcomes—visual function for near and distance activities, and vision-specific dependency—than those who had PDT.² This article offers an update of that information, which may help guide our clinical decisions.

VISION-RELATED QUALITY OF LIFE: ANCHOR

To measure vision-related quality of life, we used the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), which consists of at least 25 questions (11 subscales), administered by a trained interviewer. Scores range from 0 (worst) to 100 (perfect visual function). The AREDS group helped determine what might be a clinically relevant change on NEI VFQ scores.³

Three of the 11 subscales used for the ANCHOR trial were judged important in AMD: near activities, distance

activities, and vision-specific dependency.

For near activities, patients were asked questions about reading ordinary print and newspapers, sewing, cooking, and finding objects on a crowded shelf, as in a supermarket. Questions about distance activities dealt with descending stairs in dim light or at night, going to the movies or sporting events, or enjoying programs on television. Questions related to vision-specific dependency asked if patients need assistance with specific tasks because of their vision, such as help with their check-books, shopping, or other everyday activities.

At 24 months, compared to baseline, overall scores improved for either dose of ranibizumab; scores were unchanged when PDT was given. We saw the same results in individual subscales for near, distance and vision-specific dependency: a mean improvement with ranibizumab, and either unchanged or a loss with PDT.

Are these clinically relevant changes? Investigators concluded that a change of at least 10 points would be accepted as clinically relevant in the ophthalmic community.^{3,4} This corresponds to at least a 15-letter change on the eye chart, and it corresponds to people who progressed from intermediate to neovascular AMD in the AREDS.

In the ANCHOR trial, 20% of patients given PDT as often as every 3 months had a 10-point or more gain in their overall NEI VFQ scores between baseline and 2 years.

Although that is a good outcome, the improvement with monthly ranibizumab (either dose) was better—35%. A 10-point or more loss was not very common with PDT, about 15% of the time, and was even less common with ranibizumab, giving us confidence that the mean change corresponds to a clinically relevant change.

The same is true for near activities: Scores improved with PDT but even more so with ranibizumab. In terms of losing 10 or more points on the NEI VFQ for near activities, scores were about the same for PDT and ranibizumab. This one finding does not mean that we should use verteporfin. We must evaluate all the data together, including the visual acuity data.

We saw the same results with distance activities: a 10-point or more gain and not a lot of people losing 10 or more points on the NEI VFQ.

For vision-specific dependency, between baseline and 2 years, we saw a clinically meaningful change in about 18% of patients receiving PDT and almost twice as many of those receiving ranibizumab. These additional data give us greater confidence in the visual acuity letter scores in the ANCHOR trial, showing better outcomes with ranibizumab than with PDT.

We also considered whether the better eye or the worse eye was treated. Why is this important? When we ask patients about their visual function via questionnaire, they tell us about their visual function using both eyes. We often would presume that the better-seeing eye would drive changes in the visual function questionnaire. If the better-seeing eye is 20/25 and the other eye is 20/400, the NEI VFQ responses may be influenced by the 20/25 eye. As long as that eye stays 20/25, will the function change very much, even if the 20/400 eye drops to 20/500 or 20/640?

There were not a lot of better-seeing eyes (20/80) in the ANCHOR trial (<50%). Approximately one-third of the cases were randomly assigned to PDT; one-third were assigned to the 0.3-mg dose of ranibizumab, and about 25%, 34 eyes, were assigned to the 0.5-mg dose.

What we know from the visual acuity outcomes is now confirmed when we are treating the better-seeing eye [with ranibizumab].

For near activities, we saw about a 15- to 20-point change when the better-seeing eyes were given ranibizumab. The worse-seeing eyes had very little difference.

For distance activities, overall, we saw a 5-point increase, which is a relevant increase, because a lot of people within that 5-point increase had a 10-point or more gain, or avoided a 10-point or more loss. When the better-seeing eye was treated, however, there was a big difference and a loss with PDT. When the worse-seeing eye was treated, there was not much of a difference.

We saw similar results for vision-specific dependency.

VISION-RELATED QUALITY OF LIFE: MARINA

The MARINA trial proved that, compared with sham, monthly ranibizumab treatment provided a visual acuity benefit for minimally classic or occult with no classic lesions that had presumed recent disease progression.⁵ Investigators also reported better quality-of-life outcomes.

We see a slightly different story in MARINA, however, when the better-seeing eye was treated. For these eyes,

there was a marked difference from the sham group. Even when the worse-seeing eye was treated, there was about a 9- or 10-point difference in the means.

When the worse-seeing eye was treated, a patient's perception of his visual function changed somewhat. This was true for near and distance activities, and for vision-specific dependency. We saw a difference for the worse-seeing eyes, and a bigger difference for the better-seeing eyes.

PATIENTS' PERCEPTIONS SUPPORT VISUAL ACUITY DATA

What do these data mean? If we are treating the better-seeing eye, compared with PDT or sham, ranibizumab is more likely to change the patient's perception of near activities, distance activities and vision-specific dependency. What we know from the visual acuity outcomes is now confirmed when we are treating the better-seeing eye.

What about when we are treating the worse-seeing eye with predominantly classic lesions? In these cases, compared with PDT, we were not able to show that ranibizumab leads to a change in the patients' perceptions. Had we not treated them, however, there might have been a big difference, but we were comparing it to PDT in the worse-seeing eye. Should this influence our decision about treating someone with a predominantly classic lesion in the worse-seeing eye because we do not see a quality-of-life benefit? I would say no.

Remember that in the ANCHOR trial, the visual acuity outcomes were better, even when we treated the worse-seeing eye. In addition, the MARINA trial did show a difference in quality-of-life outcomes for the worse-seeing eye. ANCHOR showed a quality-of-life improvement for the better-seeing eye, and ANCHOR showed that, even if we did not see a difference, it does not mean there would not be a difference if we looked at many more cases.

The collective data tell us it is better to treat a predominantly classic case with ranibizumab than with PDT. That is why we would emphasize that it is probably beneficial to treat the worse-seeing eye. When treating either the better- or the worse-seeing eye, we would likely choose ranibizumab over PDT for predominantly classic lesions, and we would likely choose ranibizumab over sham for minimally classic or occult with no classic lesions. ■

1. Brown DM, Kaiser PK, Michels M, et al.; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432-1444.
2. Chang TS, Bressler NM, Fine JT, Dolan CM, Ward J, Klesert TR; MARINA Study Group. Improved Vision-Related Function After Ranibizumab Treatment of Neovascular Age-Related Macular Degeneration. *Arch Ophthalmol*. 2007;125:1460-1469.
3. Lindblad AS, Clemons TE. Responsiveness of the National Eye Institute Visual Function Questionnaire to progression to advanced age-related macular degeneration, vision loss, and lens opacity: AREDS Report no. 14. *Arch Ophthalmol*. 2005;123:1207-1214.
4. Miskala PH, Hawkins BS, Mangione CM, et al. Responsiveness of the National Eye Institute Visual Function Questionnaire to changes in visual acuity: findings in patients with subfoveal choroidal neovascularization—SST Report No. 1. *Arch Ophthalmol*. 2003;121:531-539.
5. Rosenfeld PJ, Brown DM, Heier JS, et al.; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-1431.

Applying Clinical Trial Data in Daily Practice

Results from Cohort 1 of the SAILOR Study

BY DAVID S. BOYER, MD



We are all familiar now with the positive outcomes that have been obtained using ranibizumab (Lucentis, Genentech Inc.) in the ANCHOR and MARINA trials.^{1,2} With any therapy, however, we are always con-

cerned about the risk/benefit ratio.

What follows is a summary of the 1-year data from cohort 1 of the SAILOR (Safety Assessment of Intravitreal Lucentis for Age-related Macular Degeneration [AMD]), a phase 3b study designed to evaluate the safety and efficacy of ranibizumab in treatment-naïve and previously treated patients with choroidal neovascularization (CNV) secondary to AMD.³

STUDY DESIGN AND DEMOGRAPHICS

Cohort 1 is a randomized, single-masked study of 2378 patients. The primary objective was to evaluate the safety and tolerability of intravitreal ranibizumab, as demonstrated by the incidence of ocular and nonocular serious adverse events. Other key endpoints include: the overall incidence of ocular and nonocular adverse events; the mean change in visual acuity (VA) over 12 months; and the mean total number of injections required to achieve these results.

Essentially, any patient with subfoveal CNV was eligible for treatment. Any patient who had occult or minimally classic disease, however, had to show evidence of disease progression for inclusion in the study. In this study, patients with a history of cardiovascular disease were eligible for treatment.

Previously treated or treatment-naïve patients were randomized to receive either 0.3 mg or 0.5 mg of ranibizumab. Retreatment criteria were determined at enrollment, using VA, optical coherence tomography (OCT), or both. Treatment was indicated in patients who demonstrated a 5-letter decrease from BCVA or an increase in central foveal thickness of more than 100 μ m on OCT.

Patients received treatment at day 0, month 1, and month 2. Visits were mandatory at months 3, 6, 9, and 12; however, investigators were encouraged to see patients more frequently, which they did (Figures 1 and 2).

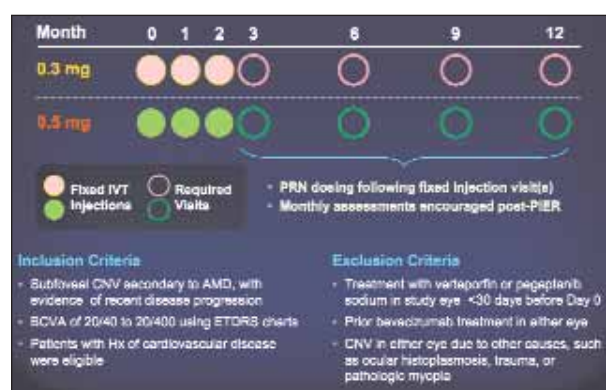


Figure 1. Treatment schema.

	0.3 mg (n=1167)	0.5 mg (n=1209)
Number of Injections* Mean $\pm$ SD	4.6 $\pm$ 1.7	4.6 $\pm$ 1.7
Number of Visits† Mean $\pm$ SD	8.8 $\pm$ 2.2	8.9 $\pm$ 2.3

* Protocol required 3 loading doses; therefore subjects subsequently received approximately 1.6 additional doses during months 3 to 11.

† Protocol required visits at Months 0, 1, 2, 3, 6, 9, 12; therefore subjects had approximately 1.8 additional visits beyond the required visits.

Figure 2. Subject treatment exposure.

The demographics of this study are similar to those of other AMD trials, ie, slightly more women, and mostly white. Approximately 40% of patients were treatment-naïve. Previously treated subjects included patients who had received pegaptanib sodium (Macugen, OSI/Eyetech), or who had undergone photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics), previous laser treatment, or intravitreal triamcinolone acetonide (Kenalog, Bristol-Myers Squibb). See Figure 3 for further information on baseline ocular characteristics.

One surprising finding was the large discontinuation rate. Eighteen percent of patients who entered the SAILOR study discontinued therapy, compared with 10%

		0.3 mg (n=1168)	0.5 mg (n=1209)
Age at Diagnosis (yrs)	Mean ± SD	77.7 ± 7.7	77.8 ± 7.8
Time Since Diagnosis (yrs)	Mean ± SD		
Treatment Naïve (n=462, 490)		0.3 ± 1.4	0.3 ± 0.7
Previously Treated (n=707, 719)		1.4 ± 2.0	1.3 ± 1.7
CNV Type	% of Subjects		
Predominantly Classic		33.1%	30.8%
Minimally Classic		23.0%	22.2%
Occult w/o Classic		41.3%	43.8%
VA (letters)	Mean ± SD		
Treatment Naïve		55.0 ± 12.5	53.8 ± 13.8
Previously Treated		48.8 ± 13.8	50.0 ± 14.3
Central Foveal Thickness (µm)	Mean ± SD	314.0 ± 109.3	314.5 ± 114.3
Total Macular Volume (mm ³)	Mean ± SD	7.8 ± 1.5	7.8 ± 1.5
IOP (mmHg)	Mean ± SD	15.5 ± 3.3	15.3 ± 3.3

Figure 3. Baseline ocular characteristics.

in the MARINA and ANCHOR trials. After further analysis, I believe discontinuation in SAILOR cohort 1 was secondary to several factors, namely:

- 1) The retreatment criteria may not have been stringent enough. As data became available to support retreatment at more frequent intervals when fluid was present, many investigators did not want to wait for patients to develop 100 µm of increased thickening. They wanted to treat earlier, so they asked patients to discontinue.
 - 2) During the study, bevacizumab (Avastin, Genentech Inc.) and ranibizumab became commercially available, so if patients required treatment, they could discontinue from the trial and still receive therapy.
- It is very important to note there was no difference in the discontinuation rate between the 0.3-mg group and the 0.5-mg group.
- I also found it interesting that the average number of injections was only 4.6, particularly considering 3 injections were mandatory. This means that over a 9-month period, only 1.6 additional injections were given. This is a very low number of reinjections to achieve the results we were able to achieve. Figure 4 shows the percentage of patients who received treatment over time.

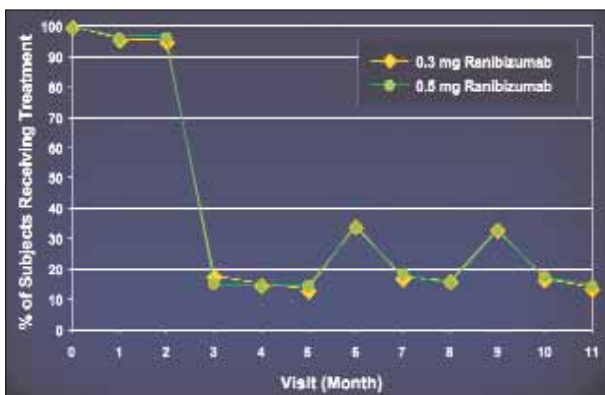


Figure 4. Percentage of subjects who received treatment over time.

SAFETY DATA—OCULAR ADVERSE EVENTS

Key serious ocular adverse events were essentially equal in the 0.3-mg and 0.5-mg groups, and this is consistent with what we have seen with other trials involving intravitreal injections, including the VISION trial and the MARINA and ANCHOR trials.^{1,2,4} When we looked at inflammation and cataract, we found a slight increase in the incidence of iritis in the 0.5-mg group (3%) compared with the 0.3-mg group (1%). This is not statistically significant and, in fact, is very small in the scheme of things.

SAFETY DATA—NONOCULAR ADVERSE EVENTS

Figure 5 summarizes nonocular adverse events.

Stroke. We evaluated 21 factors related to stroke, such as patients on coumadin, patients who had previous myocardial infarction, patients who had high lipids, and so on. Only five of those factors appeared to have a minor influence on the stroke rate:

1. Prior stroke
2. Congestive heart failure
3. Arrhythmias
4. Angioplasty
5. Valve malfunction.

Previous stroke and arrhythmia were the most obvious risk factors for stroke. I will discuss those in more detail.

Retina specialists in the US remember a “Dear Doctor” letter from Genentech in January 2007, reporting a statistically significant difference in stroke rate between patients receiving the 0.3-mg dose and those receiving the 0.5-mg dose of ranibizumab.⁵ This was based on a planned interim analysis performed by the Data and Safety Monitoring Committee, which showed that 3 patients in the 0.3-mg group and 13 patients in the 0.5-mg group ($P=.02$, statistically significant) had strokes.

When we looked at the incidence of stroke again at the end of the first year of the study in November 2007,

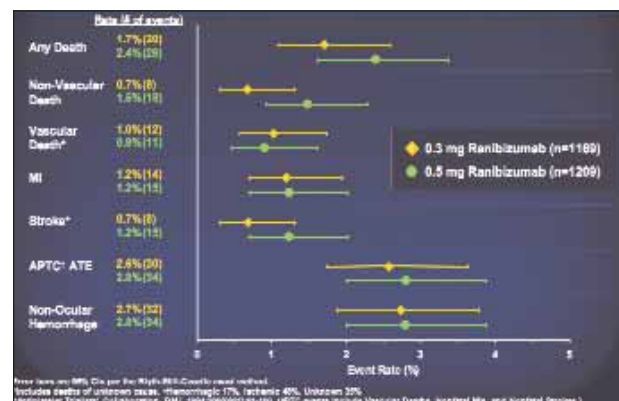


Figure 5. Key nonocular safety findings.

Emerging Data to Guide Clinical Decisions:

Dose		0.3 mg (n=1189)	0.5 mg (n=1205)	
Number (% of Deaths)		20 (1.7%)	29 (2.4%)	p=NS/NS*
Number of Prior Doses	Mean (SD)	3.2 (0.7)	3.1 (1.0)	—
Time from First Dose – All Deaths (days)	Median Mean (SD)	224 226 (88)	189 179 (94)	0.092
Time from Previous Dose – All Deaths (days)	Median Mean (SD)	127 139 (32)	65 86 (71)	0.014
Vascular and Unknown Deaths (days)	N (%) Median Mean (SD)	12 (1.0%) 132 134 (30)	11 (0.9%) 46 63 (30)	0.679
Non-Vascular Deaths (days)	N (%) Median Mean (SD)	8 (0.7%) 127 146 (72)	18 (1.5%) 83 87 (81)	0.075

* p-value for treatment differences (Kruskal-Wallis Test)

Figure 6. Time of death relative to dose.

we found no statistical difference between the groups.

Nonocular hemorrhages. Another important takeaway from the SAILOR cohort 1 data is that the incidence of nonocular hemorrhages was about 2.7% and 2.8%. In the MARINA and ANCHOR studies, the incidence was 6% to 8% for an unknown reason. In SAILOR, we have several thousand patients, and nonocular hemorrhage does not seem to be a real problem.

When we looked at the incidence of stroke again at the end of the first year of the study ... we found no statistical difference between the [0.3-mg and the 0.5 mg] groups.

Cause of death (vascular and nonvascular). Looking at vascular deaths (those that were possibly related to VEGF) there is really no difference, whether cardiovascular-related, stroke-related, or from an unknown cause.

Looking at nonvascular deaths, there was almost a doubling of the rate at the higher dose—0.7% vs 1.5%. Is there a biological reason for this, or is this just happenstance? If you look at a subgroup of patients, 5 of them

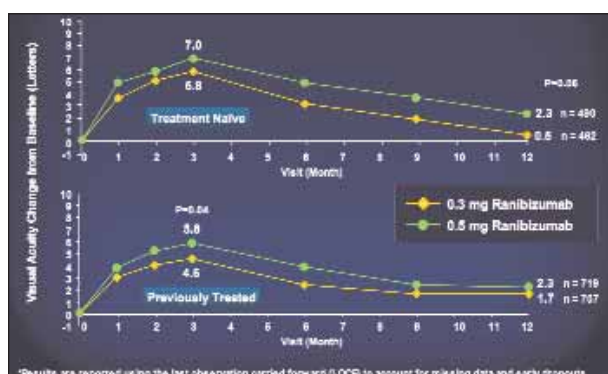


Figure 8. Mean change in visual acuity (letters) over time.

Time of stroke relative to Dose		0.3 mg	0.5 mg
Number (%) of strokes		8 (0.7%)	15 (1.2%)
No. of Prior Doses	Mean – SD	3.0 ± 1.4	3.1 ± 0.8
Days from First Dose	Median Mean (SE)	120 128 ± 63	160 157 ± 84
Days from Previous Dose	Median Mean – SD	38 59 ± 53	38 89 ± 82

Figure 7. Time of stroke relative to dose.

in the high-dose group had cancer-related deaths. Three of these patients were known to have cancer upon entering the trial. There was accidental injury in 3 patients. I think it is safe to say that if we look at deaths based on biological factors, such as VEGF, there is no difference between the two groups.

Figures 6 and 7 summarize time of death relative to dose and time of stroke relative to dose.

At the higher dose, there did seem to be a tendency for the time from the first dose and time from the previous dose to be shorter, but not statistically significant.

Time to stroke not only did not have a difference between the days from the first dose, it was actually faster if a patient received a lower dose. There was no statistically significant difference.

Ocular hypertension. Ocular hypertension is a concern because it can be modified by VEGF. There was no increased risk of hypertension in the high-dose group versus the low-dose group.

Compared to other studies—MARINA, ANCHOR, FOCUS, and PIER⁶—the arterial thrombotic event data from the SAILOR study were the same. The stroke rate was what we expected and actually less than what has been reported by Medicare for the same group of patients.⁷

EFFICACY DATA

Patients in cohort 1 of the SAILOR study received 3 doses of ranibizumab, and at month 3, they could receive

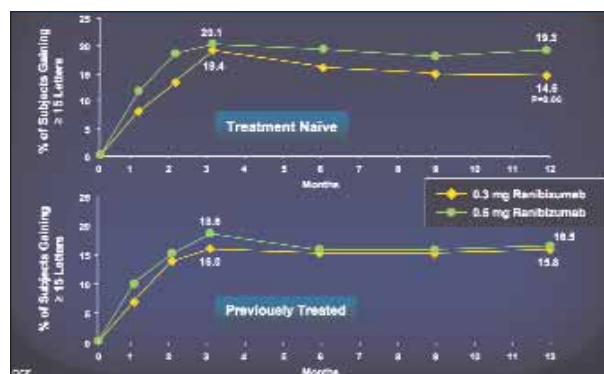


Figure 9. Percentage of subjects gaining ≥15 letters over time.

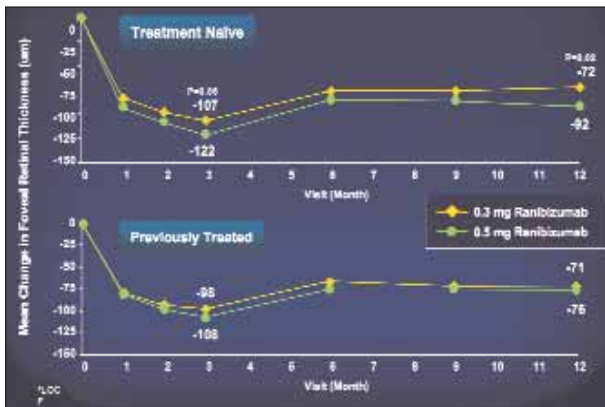


Figure 10. Mean change in central foveal thickness over time.

an additional dose if they met the criteria. Vision improvement was somewhat better in the treatment-naïve group than in the previously treated group. The 0.5-mg dose gave a 1- or 2-letter improvement over the 0.3-mg dose, but the outcomes are remarkably similar (Figure 8). Previously treated patients showed 5.8 letters of improvement in the 0.5-mg dose and 4.6 letters in the lower dose. Unfortunately, these results did not carry through as the study continued.

SAILOR cohort 1 data showed the incidence of nonocular hemorrhages was about 2.7% and 2.8%. In the MARINA and ANCHOR studies, the incidence was 6% to 8%.

Looking at the percentage of patients who gained 3 lines of vision, however, you can see the rapid uptake at month 3 and then stabilization, again, better in the high dose and better in the treatment-naïve group (Figure 9). This would be expected because patients who were not previously treated would have less damage to the pigment epithelium and the choroid.

Regarding the mean change in central foveal thickness over time, the graph is almost the reverse of the VA graph (Figure 10). We can see the maximum improvement on OCT, again treatment-naïve better than previously treated, and a better response with the high dose than with the low dose.

Comparing these efficacy results to those from the other studies, we can see that they are somewhat better than the PIER data, but not as good as the ANCHOR and MARINA data, either for the number of patients gaining 15 letters or 3 lines of vision, or the percentage of change in letters over time.

STUDY LIMITATIONS

The SAILOR study has limitations, and it is important to point those out. One was that the required dosing schedule was not currently used in clinical practice, and this resulted in many fewer injections than were administered in previous trials. This may have affected the safety and efficacy results, and contributed to the higher-than-expected dropout rates. Today, based on new data, we treat much more frequently if we see fluid present in the retina.

Another limitation was that there was no control arm in this study.

SAFETY AND EFFICACY DATA SUMMARY

In summary, the dose groups were equivalent in the overall rate of the Antiplatelet Trialists' Collaboration (APT) events, myocardial infarctions, and vascular deaths. There was a trend toward higher stroke and nonvascular death rates in the 0.5-mg group, but these were not statistically significant. Prior stroke was the most significant risk factor for stroke. Although the numbers were small, there was a trend for a higher rate in the 0.5-mg dose group than in the 0.3-mg dose group among subjects with this risk factor. Ocular safety was consistent with both doses and with the prior trials.

Visual acuity increased over the first 3 injections and then decreased through month 12, a trend similar to that observed in the PIER study. The percentage of patients who gained ≥ 15 letters increased during the first 3 months and then tended to be maintained at 15% to 19% through month 12, which is a big difference from what was reported in the MARINA (30%) and ANCHOR (40%) trials. Treatment-naïve subjects tended to do better than previously treated subjects, which we would expect. As in previous trials, there was a consistent trend for the 0.5 mg-dose to be more efficacious than the 0.3-mg dose.

The results of the SAILOR 1 study have given us further confidence in the systemic safety of ranibizumab. The study also suggests that more frequent injections may be necessary to achieve the best visual results. ■

1. Brown DM, Kaiser PK, Michels M, et al.; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432-1444.
2. Rosenfeld PJ, Brown DM, Heier JS, et al.; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-1431.
3. Boyer DS. SAILOR safety outcomes at one year: Does ranibizumab increase the risk of thromboembolic events? Presented at: The Bascom Palmer Eye Institute Angiogenesis, Exudation and Degeneration meeting, Feb. 23, 2008, Key Biscayne, FL.
4. VEGF Inhibition Study in Ocular Neovascularization (VISION) Clinical Trial Group, Chakravarthy U, Adamis AP, Cunningham ET Jr, et al. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology*. 2006;113:1508-1521.
5. Genentech Inc., Dear Health Care Provider Letter, Jan. 24, 2007.
6. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol*. 2008;145:239-248.
7. Fung AE. Rates of arterial thromboembolic events in Medicare patients with neovascular AMD vs. age-matched controls. Presented at: The Bascom Palmer Eye Institute Angiogenesis, Exudation and Degeneration meeting, Feb. 23, 2008, Key Biscayne, FL.

Implementing Intravitreal Injections in Clinical Practice

A discussion of injection logistics for safety, comfort and efficiency.

BY NANCY HOLEKAMP, MD



In the past 5 years, retina specialists have experienced a tectonic shift in how we practice, specifically, a remarkable increase in the number of intravitreal injections performed in our offices. We are injecting numerous different agents, sometimes several at the same time. In addition, we are injecting for conditions other than neovascular AMD, such as diabetic retinopathy, vein occlusions, and neovascular glaucoma.

Busy is good, but how do we adjust our practices to accommodate the increased volume?

Our group at the Barnes Retina Institute in St. Louis includes 7 private-practice and 4 university-employed retina specialists, and we all perform injections differently. On any given clinic day, I may see about 50 patients and perform about 10 injections, which means I am injecting 1 of every 5 patients I evaluate. This can really slow your flow if you do not have a good system.

I will share my personal approach to injection logistics as a means of illuminating some issues that we all are encountering.

NEW-ONSET EXUDATIVE AMD

When I see a patient with new-onset exudative AMD, I perform a baseline fluorescein angiogram. After I have confirmed the diagnosis, my first-line therapy is either monthly ranibizumab or bevacizumab, and I will discuss both drugs with the patient.

When a patient consents to monotherapy anti-VEGF injections, I will inject 90% to 95% of cases that same day. This approach is more convenient for the family member who had to take off work to bring the patient to the office, and it is also more efficient for my staff and me. The patient is present and dilated, and half the paperwork has been done. Additionally, many of these patients realize they are losing vision and want the injection the same day.

INJECTION PROTOCOL

As I leave the examination room, I hand the chart to my assistant and say, "We are going to give an injection." Then, all this "magic" happens that I never see. My

We are injecting numerous different agents, sometimes several at a time. In addition, we are injecting for conditions other than neovascular AMD, such as diabetic retinopathy.

staff calls the insurance company for preapproval, has the patient sign an advance beneficiary notice and informed consent, and provides the patient with photocopies of these documents as well as printed information on AMD. While this is happening, I am seeing other patients.

My staff notifies me when the patient is in the treatment room, ready for the injection. When I arrive, the patient is lying on the procedure table, the anesthetic drops have been given, and the drug is out and ready. The first order of business is to call a time-out to verify the eye and the drug.

Once the patient, the staff and I agree on the eye and drug, I draw up the drug in the syringe. I provide additional anesthetic with a lidocaine-soaked cotton pledget, and apply betadine to the eye. (I am unique in that aspect in our practice.) Then, I give the injection, sign the paperwork, and leave. The procedure takes less than 2 minutes. As I am leaving, the staff is washing the betadine out of the eye, offering reassurance to the patient, and giving postoperative instructions.

Taking extra time for safety is very important, so let's examine these steps more closely. First, we have a practice-wide policy whereby the physician draws up the drug. We instituted this policy because of a medication error when a technician drew up ranibizumab instead of bevacizumab. Second, there is nothing worse than finishing the injection and having the patient say, "Gee, I thought it was the other eye." The patient, staff and I have to agree in advance on the eye that is being injected.

Ethical Considerations

BY NANCY HOLEKAMP, MD

Based on level 1 evidence from large, randomized clinical trials, anti-VEGF therapy, namely ranibizumab (Lucentis, Genentech Inc.), is the new standard of care for treating exudative AMD.^{1,2} At the same time, however, “standard of care” can be defined differently. In legal terms, for example, standard of care may be determined by what a reasonable physician in your area would do in a similar situation based on available information. Bevacizumab (Avastin, Genentech Inc.) has gained acceptance in this fashion.

How do you decide which drug to use? Despite multiple confounding factors, such as cost, perceived advantages or disadvantages, personal bias, and conflicts of interest, the patient always comes first.

Providing informed consent aids the decision-making process between physician and patient. If I were giving informed consent about ranibizumab, I might say it is effective in two large clinical trials, but it is expensive. Multiple injections may be needed, and we would need to find out how much insurance will nor will not cover. If I were giving informed consent about bevacizumab, I might point out that it is not approved by the FDA for eye disease—it is not even formulated for intravitreal injection—but it is being used all over the world. Hundreds of thousands of injections are being given, and it appears to be safe and effective. In our practice, we still use a bevacizumab-specific informed consent that we download from the Ophthalmic Mutual Insurance Company (OMIC) Web site.

I think it is safe to say that photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics) monotherapy, pegaptanib sodium (Macugen, OSI/Eyetech) monotherapy, and subfoveal laser are inferior treatments for AMD. Other therapies, such as combinations of PDT and bevacizumab or dexamethasone, are promising, very provocative, very exciting, but right now, they are nonvalidated in prospective, randomized clinical trials.

The following AMD cases represent some of these ethical dilemmas.

WHO DECIDES TO TREAT AND WHY?

A patient was referred to a Veterans Administration (VA) retina clinic from a more rural VA clinic. The 69-year-old man had a predominantly classic lesion, 20/400 vision in his better-seeing eye, and a large disciform scar on the fellow eye.

My retina fellow evaluated the patient, made the diagnosis, and recommended ranibizumab. In this instance, the patient was returning later for the ranibizumab. A few days later, the fellow learned that the injection appointment had been canceled. As it turns out, each VA hospital pays for treatments for its own patients, regardless of where the treatment is performed. The optometrist who was the department chief at the referring hospital said he thought ranibizumab was too expensive, and he instructed the rural VA to cancel the treatment.

When my fellow asked for my advice, I said, “Obviously, you have to call the optometrist and the patient, and you have to plead your case for treating this patient in the way that you originally recommended.”

The VA is committed to providing veterans with the very best medical care our society can offer. The patient received the injection.

GRID LASER OR VITAMINS?

A 67-year-old patient presented for a second opinion. She had 20/25 visual acuity, soft, confluent drusen, and some areas of hyper- and hypopigmentation. A local retina specialist recommended grid laser for the drusen. Perhaps he felt he was executing his ethical responsibility, because he gave the patient informed consent, explained that grid laser was not FDA approved, and told her that she would have to pay \$2000 out of pocket.

I told the patient that this study has been done, and the results were found not to be of benefit.⁴ I recommended she not have the laser. In fact, I explained a more appropriate course of action would be to take high-dose vitamin supplementation according to the AREDS study⁵, or to enroll in the AREDS 2 clinical trial.

PRIVATE-LABEL RIP-OFF

A 73-year-old patient who has intermediate drusen and a strong family history of AMD transferred her care because her retina specialist was retiring. Her medication list included a product whose name suggested it was for macular health.

According to the label, this dietary supplement included vitamins C and E, beta-carotene, and zinc, but not in the doses studied in the AREDS. I told the patient I have no information on these vitamins in these doses, but I do know about the AREDS-recommended vitamin doses, and

Emerging Data to Guide Clinical Decisions:

ENSURING PATIENTS' COMFORT

Taking extra steps to minimize pain is very important. In my opinion, the betadine, which is toxic to the corneal epithelium, can be painful. If it stays on the eye for a prolonged period or dries on the surface of the eye, patients will have surface ocular pain later. I apply betadine myself just prior to the injection, and I always have my staff rinse off the betadine after the injection.

A subconjunctival injection of lidocaine is not my preference because it makes the procedure bloodier, adds another step, and opens the door to a medication error.

Another measure to minimize pain is to apply an anesthetic-soaked cotton pledget to the injection site for about 10 to 20 seconds. Alternatively, you could give a subconjunctival lidocaine injection. A lidocaine injection is not my preference, however, because it makes the procedure bloodier, adds another step, and opens the door to a medication error because there are now two syringes filled with clear fluid (lidocaine and drug). It is not unheard of that the drug was injected subconjunctivally and the lidocaine was given intravitreally.

PREVENTING INFECTION

We know the infection rate for intravitreal injections for AMD is very low.¹ That may be because most of us agree that two things are absolutely essential: the betadine prep and the lid speculum.²

Questions remain, however, about whether or not

pre- or postinjection antibiotics are necessary. I inject enough patients on the day that they present to me that I am fairly confident that preinjection antibiotics are not necessary. In our practice, we use postinjection antibiotics, but I have no data to support that. Our practice is waiting for information from peer-reviewed literature so we can abandon that practice, as I believe it is probably not necessary.

ENSURING COMPLIANCE

Many of us worry about patients returning on a monthly basis for injections if we deem them necessary. About 30% to 40% of my patients are experiencing vision improvement, and the majority are at least staying the same, so compliance is not usually a problem. Patients want to come back.

In my practice, we do not see patients between injections. We reached this decision after surveying other large retina groups and learning there were not many problems. We still call each patient after the first injection to see how he or she is doing, and we give patients large-print post-injection instructions to call us for increased pain or decreased vision.

CHOOSE YOUR PROTOCOL

I have described some strategies that have evolved as I have implemented intravitreal injections in my practice. As mentioned, in my group we have 11 doctors giving intravitreal injections in 11 different ways. But one thing is similar across the board: Patients are benefiting. ■

1. Pilli S, Kotsolis A, Spaide RF, et al. Endophthalmitis associated with intravitreal anti-vascular endothelial growth factor therapy injections in an office setting. *Am J Ophthalmol*. 2008;145:879-882.

2. Aiello LP, Brucker AJ, Chang S, et al. Evolving guidelines for intravitreal injections. *Retina*. 2004;24(Suppl):S3-S19.

I recommended she take those. Interestingly, the retina specialist sold the supplement to her for \$100 per month.

UNREASONABLE MARK-UP

A retina specialist obtains bevacizumab from a licensed compounding pharmacy for \$27 per syringe. He charges non- or underinsured patients \$450 per dose plus the injection fee of \$200, obviously ignoring the American Academy of Ophthalmology code of ethics, which says that reasonable fees should be charged for the services provided.

PUTTING PATIENTS FIRST

The litmus test of ethical behavior in ophthalmology is acting in the best interest of the patient. We must provide

complete informed consent, commit to evidence-based medicine, and when it is not available, help generate rigorous scientific data via the appropriate pathways. For the noncovered services and the off-label uses, we must charge reasonable fees. ■

1. Brown DM, Kaiser PK, Michels M, et al. ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432-1444.

2. Rosenfeld PJ, Brown DM, Heier JS, et al. MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-1431.

3. Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Laser treatment in patients with bilateral large drusen: the complications of age-related macular degeneration prevention trial. *Ophthalmology*. 2006;113:1974-1986.

4. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. *Arch Ophthalmol*. 2001;119:1439-1452.

Persistent Challenges in AMD Management

As new treatment options emerge, clinicians must weigh safety, efficacy, and much more.

BY JULIA A. HALLER, MD



Treatment issues for AMD continue to emerge, even though we know how effective anti-VEGF therapy can be. The foremost question for most of us is: What is the optimum treatment regimen? This is followed in

quick succession by: How do you decide when to retreat? Do you use optical coherence tomography (OCT) or fluorescein angiography or both, and when?

Other questions that continue to arise are: What is the role of treatments other than ranibizumab (Lucentis, Genentech, Inc.)? How about bevacizumab (Avastin, Genentech Inc.), photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics), and steroids? Do you use just 1, 2 or all 3? Also, how do you manage cases that were specifically excluded from the trials, such as pigment epithelial detachments (PEDs), retinal angiomatous proliferation (RAP) lesions or hemorrhages? For these patients, treatment is an extrapolation of study results of the mainline data.

Let's start with optimum treatment regimens. How do we decide when to retreat, and what tests help us?

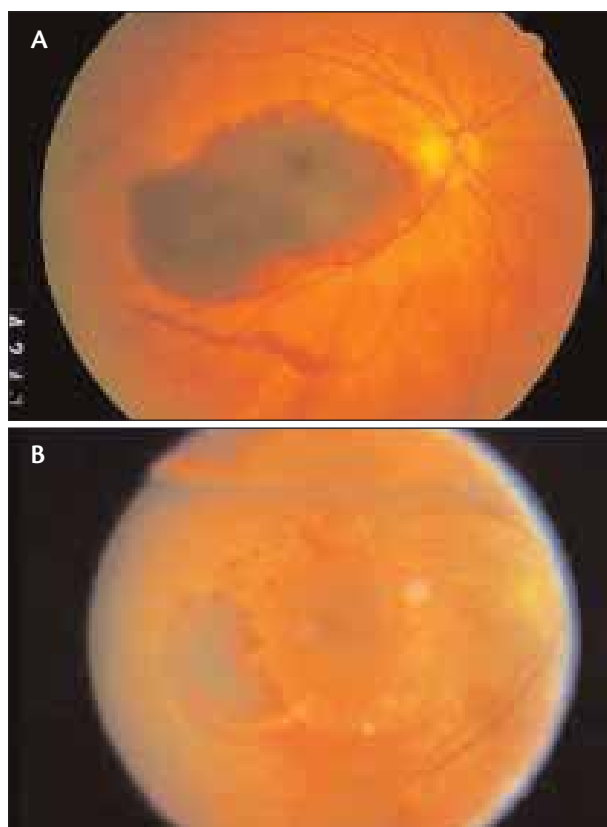
AUDIENCE RESPONSE

[Editor's note: The number of respondents ranged from 36 to 55 per question.]

When we polled our audience about retreatment with ranibizumab, we learned that, by far, the majority of respondents are using a PrONTO-type approach¹; 12% follow the PIER guidelines²; 9% use monthly injections; and 19% are using some other type of modality.

Regarding imaging for follow-up, 57% of respondents are using OCT primarily, 40% are using a combination of OCT and fluorescein, and 3% are basically gestalting it in some other way. No one in this audience is using solely fluorescein primarily.

Seventy percent of respondents are not using combination therapy. Of the 30% who are using combination therapy, 35% are using PDT with verteporfin and an anti-VEGF agent; 23% are using so-called triple therapy with PDT, an anti-VEGF agent and a steroid. Another



Figures 1A and 1B. Subretinal Hemorrhage—Case 1

19% are using some other anti-VEGF combination. No one in this audience is using PDT plus steroid.

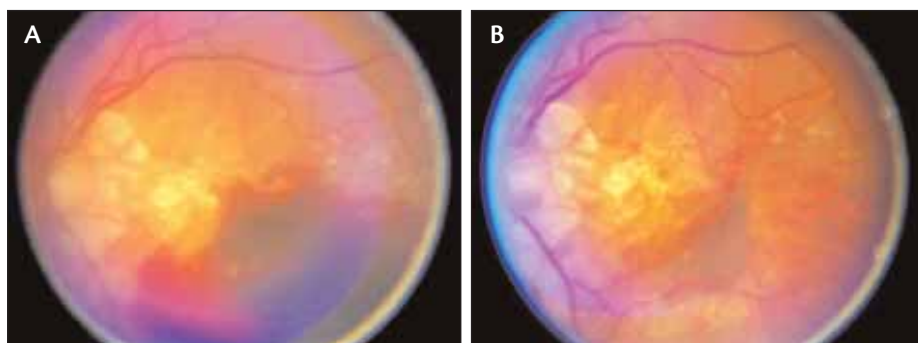
I think the take-home message is that there is a lot we do not know, and people are trying to find their way.

Let's discuss some cases similar to those that were excluded from the trials.

SUBRETINAL HEMORRHAGE

Eyes with subretinal hemorrhage may be treated with either observation alone, anti-VEGF therapy, PDT through thin blood in selected cases, pneumatic displacement of hemorrhage with or without adjunctive

Emerging Data to Guide Clinical Decisions:



Figures 2A and 2B. Subretinal Hemorrhage—Case 2

intravitreal tissue plasminogen activator (tPA), vitrectomy with extraction of hemorrhage and choroidal neovascularization, vitrectomy with subretinal tPA injection, or a combination of therapies. Data from the Submacular Surgery Trials indicated that surgery as performed in that study was not better than observation in terms of visual outcome, at least for eyes with extensive hemorrhage and lower levels of acuity.³

Case 1 (Figures 1A and 1B) shows a patient who was treated with pneumatic displacement of subretinal hemorrhage.^{4–6} Tissue plasminogen activator and an intravitreal gas bubble were injected. Two days later, the blood had cleared from the macular center, and the patient's vision had returned to the 20/30– level.

Of course, there are many other presentations and methods for treating subretinal hemorrhage.

Case 2 (Figure 2A) shows a 90-year-old man whose vision dropped suddenly to the count fingers level in this eye. He has a disciform scar in the other eye. The patient was treated with injection of subretinal tPA.

The next day, all of the blood had gone inferiorly, and vision recovered to the 20/50– level. He has a temporal RPE tear (Figure 2B).

In summary, then, although we have a number of different ways of treating subretinal hemorrhage, it is not clear at all what the best way is. For this diagnosis, all we can do at present is individualize treatment to the best of our ability, and actively pursue further research.

THE NEXT FRONT: DRY AMD

Now that we have more effective treatments for wet AMD, another topic that has risen higher on our radar screen is dry AMD, because even after we have successfully treated wet AMD, progressive dry AMD continues to be a problem.

As we follow more eyes after anti-VEGF therapy, many of us have patients whom we chalked up in the win category, only to find a year or more later, even without recurrence, a gradual tapering of vision due to progressive atrophy. We know that when we look at these dry

foveas, the retinal tissue is thinner and more atrophic, and this is an ongoing challenge.

NEW DRUG DEVELOPMENT

Issues for drug development in the wake of anti-VEGF miracles include numerous factors. It is difficult to know what constitutes “better” now. If

ranibizumab stabilizes more than 90% of patients and improves 40%, that bar is so high that it is very difficult to bring other drugs into testing. In fact, we know that a number of companies have dropped out of the market.

There are still unmet needs, and we face these every day. We need longer-lasting drugs; we need ways to maintain or restore 20/20 vision for everyone; we need drugs to treat dry AMD; and we need ways of treating hemorrhage and aggressive lesions.

New delivery options are very much needed, including formulations that could potentially help us with long-term delivery.

FUTURE THERAPIES

Looking to the future, we are interested in pursuing customized treatment for each patient's individual disease process. We likely will be using multidrug regimens, and genetically profiling patients. Many of you probably saw the recent online publication in the *New England Journal of Medicine*, reporting successful results using gene therapy for Leber's congenital amaurosis in a small group of patients.⁶ This and other very exciting work suggest we are entering a whole new era. ■

1. Lalwani GA, Fung AE, Michels S, et al. An OCT-guided variable-dosing regimen with ranibizumab (Lucentis) in neovascular AMD: two year results of the PrONTD study. Poster presented at: The Annual Meeting of the ARVO; May 7, 2007; Fort Lauderdale, FL.

2. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol*. 2008;145:239–248.

3. Bressler NM, Bressler SB, Childs AL, et al. Submacular Surgery Trials (SST) Research Group. Surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: ophthalmic findings: SST report no. 13. *Ophthalmology*. 2004;111:1993–2006.

4. Ogawa T, Kitaoka T, Mera A, Saitoh AK, Amemiya T. Treatment for subretinal hemorrhage in the macula: pneumatic displacement of hemorrhages. *Retina*. 2000;20:684–685.

5. Tennant MT, Borriello JL, Regillo CD. Management of submacular hemorrhage. *Ophthalmol Clin North Am*. 2002;15:445–452.

6. Bainbridge JWB, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. *N Engl J Med*. 2008;358:2231–2239.

Emerging Data to Guide Clinical Decisions: Treating the AMD Patient

INSTRUCTIONS FOR CME CREDIT

1 AMA PRA Category 1 Credit™

Expires July 2009

CME credit is available electronically via www.dulaneyfoundation.org.

To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses." If you are experiencing problems with the online test, please e-mail us at support@dulaneyfoundation.org and explain the details of any problems you encounter with the Web site. Alternatively, you can fax your exam to us at +1-610-771-4443. Indicate how you would like to receive your certificate below. Please type or print clearly or we will be unable to issue your certificate.

Name _____ ☐ MD participant ☐ non-MD participant

Phone (required) _____

I would like my certificate sent via ☐ fax _____

I would like my certificate sent via ☐ email _____

CME QUESTIONS

1. According to Neil M. Bressler, MD, when investigators used the NEI VFQ-25 to assess vision quality in the ANCHOR trial, which of the following was found at 24 months compared to baseline?

- a. An improvement in the overall score for the lower dose of ranibizumab (Lucentis, Genentech Inc.).
- b. An improvement in the overall score for the higher dose of ranibizumab.
- c. An improvement in the overall score for either dose of ranibizumab.
- d. An improvement in the overall score for photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics)

2. According to Dr. Bressler, investigators concluded a change of at least how many points in the NEI VFQ-25 score would be accepted in the ophthalmic community as a clinically relevant change?

- a. 5 points
- b. 10 points
- c. 15 points
- d. 20 points

3. According to Dr. Bressler, what percentage of patients administered either dose of ranibizumab monthly in the ANCHOR trial had a 10-point or more gain in their overall NEI VFQ scores between baseline and 2 years?

- a. 15%
- b. 25%
- c. 35%
- d. 45%

4. According to David S. Boyer, MD, what percentage of patients who entered the SAILOR trial discontinued therapy?

- a. 4%
- b. 8%
- c. 12%
- d. 18%

5. According to Dr. Boyer, at the end of the first year of the SAILOR trial (November 2007), which of the following was reported?

- a. An increased incidence of stroke in patients receiving the 0.3-mg dose of ranibizumab
- b. An increased incidence of stroke in patients receiving the 0.5-mg dose of ranibizumab
- c. No statistical difference between the two groups
- d. Stroke rate was not evaluated

6. According to Dr. Boyer, how did the incidence of ocular hemorrhage in the SAILOR trial compare to what was observed in other trials?

- a. The incidence of nonocular hemorrhages was less than in MARINA and ANCHOR.
- b. The incidence of nonocular hemorrhages was more than in MARINA.
- c. The incidence of nonocular hemorrhages was more than in ANCHOR.
- d. The incidence of nonocular hemorrhages was about the same in all trials.

7. According to Dr. Boyer, in the SAILOR trial, visual acuity increased with the first 3 injections and then decreased through month 12, which is a trend similar to that observed in what other study?

- a. ANCHOR
- b. MARINA
- c. PIER
- d. VISION

8. To minimize pain for her patients, which of the following steps has Nancy Holekamp, MD, taken?

- a. She does not use betadine.
- b. She applies an anesthetic-soaked cotton pledget to the injection site for about 10 to 20 seconds.
- c. She uses subconjunctival lidocaine injection.
- d. None of the above

RETINA TODAY