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Article

Fine-Tuning Your Anti-VEGF Injection Protocols

The second article in our series recapping research and analysis presented at our annual meeting

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RPS: From the Podium to the Practice

Fine-Tuning Your Anti-VEGF Injection Protocols

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ANDREW E. MATHIS, PhD, MEDICAL EDITOR

This issue, we will be covering four presentations from the 5th Annual *Retinal Physician* Symposium, which took place in the Bahamas from March 25 to March 28, 2009. Two of the presentations look at anti-VEGF drugs for AMD — particularly regarding their safety and finding an optimal dosing strategy. Keeping AMD in mind, we also present a lecture on lesion size and grading. Finally, we offer a discussion of practice management considerations, with an eye toward lowering costs and increasing revenue.

DAVID BOYER ON THE SAFETY OF ANTI-VEGF DRUGS

There's little question that anti-VEGF drugs are effective in treating conditions such as age-related macular degeneration, but what safety concerns arise? This was the topic of a presentation at the *Retinal Physician* symposium by David S. Boyer, MD, a retinal physician in private practice in Los Angeles.

Dr. Boyer pointed to the case of Merck's NSAID Vioxx, which is believed to have caused roughly 100,000 heart attacks before it was withdrawn from the market in 2004. The potential problem with anti-VEGF drugs, Dr. Boyer continued, is that VEGF is a naturally occurring chemical signal that is necessary for normal function in several bodily systems. A drug such as ranibizumab will not only block excess levels of VEGF, but it may block VEGF levels to such an extent that they fall below normal levels needed for proper function. This occurs systemically and is not limited just to the eye. Plus, VEGF is a neuroprotectant and may have roles in treatment of Alzheimer's disease and epilepsy.

Referring to the age of AMD patients, Dr. Boyer said, “The people that we're dealing with are a sick group of patients.” He cited the higher risks of stroke, hypertension and elevated cholesterol in the AMD patient group, not to mention the increase in rates of stroke among participants in the SAILOR trial. This may have constituted a safety signal, Dr. Boyer said, warranting further investigation into the safety of anti-VEGF drugs.

Also, Dr. Boyer pointed to another key safety consideration to be taken into account when using anti-VEGF drugs — progression of geographic atrophy despite a halt in the wet form of AMD. This is a cause of vision loss in patients despite initial improvements after treatment with anti-VEGF drugs, and may be related to the effects of anti-VEGF drugs on the choriocapillaris **(Figure 1)**.

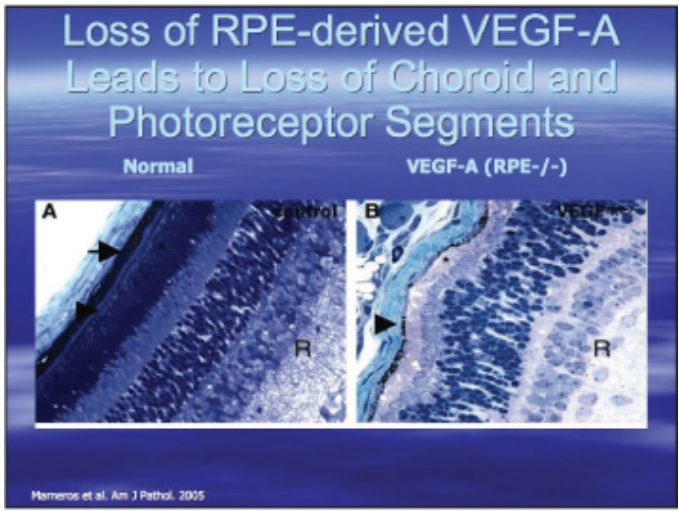

Figure 1. Suppression of VEGF-A has a negative effect on photoreceptors and other ocular anatomy.

The first data set Dr. Boyer looked at was the VISION trial of Macugen for wet AMD. He noted that, in this trial, there did not seem to be either a problem with progression of geographic atrophy or serious adverse events. Nevertheless, the problem of the adverse events in the ANCHOR and MARINA trials remained disconcerting. Genentech conducted the SAILOR trial to better determine if there were any systemic or ocular adverse events that would be exposed from analyzing a larger cohort of patients.

Patients in the SAILOR trial were divided into two cohorts: The first were given injections of ranibizumab of either 0.3 mg or 0.5 mg, while the second were given 0.5 mg injections only. Dr. Boyer stressed that these injections were not given for efficacy as that had already been demonstrated.

The cohorts differed further in terms of how often injections were given. Cohort 1 received a mandatory three treatments and then were retreated based on changes in visual acuity or retinal thickness. Cohort 2 was on no fixed dosing schedule and retreatment was based on the judgment of the individual investigator.

First, Dr. Boyer noted the high dropout rates in both cohorts (18% in cohort 1 and 50% in cohort 2). Dr. Boyer chalked up the rate to three factors: (1) The availability of bevacizumab, (2) The ability of some patients to receive injections covered by their own insurance policies, and (3) The unwillingness of some investigators to wait for the required 100-µm increase in retinal thickness before retreatment could occur.

Presenting an overview slide of all nonocular serious adverse events in the SAILOR trial, Dr. Boyer showed the audience that the incidence of all side effects was very low. That point notwithstanding, Dr. Boyer pointed out that death rates, particularly for nonvascular death, were higher in patients receiving 0.5-mg doses, though this was not felt to be related to anti-VEGF therapy. Further, arterial thrombolic events were higher than other serious adverse events in patients in both cohorts.

Focusing on stroke rate, the highest incidence was among former stroke patients who were in cohort 1 and receiving 0.5-mg injections (**Figure 2**). However, Dr. Boyer noted, the differences were not statistically significant and thus no conclusive statements could be made about stroke risk. This was further emphasized by the fact that, if a patient had not had a previous stroke, he or she was far less likely to experience a stroke during the study period. Arrhythmias were slightly more common in all groups, but incidents of congestive heart failure were not

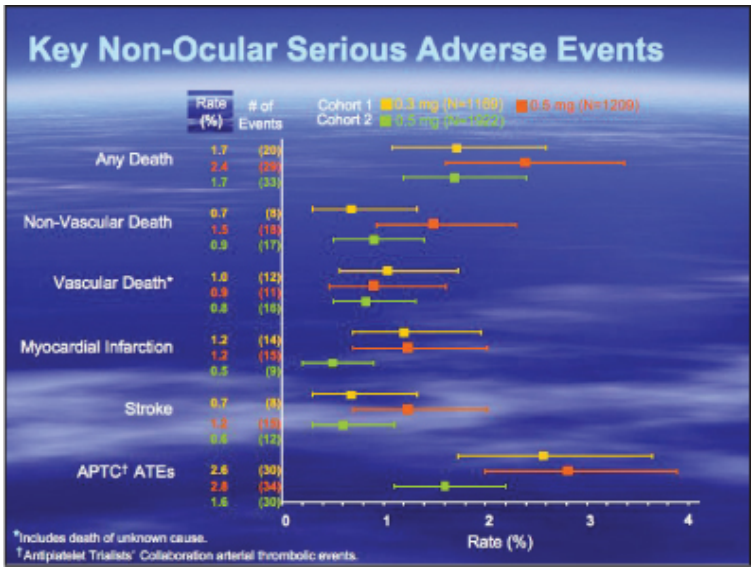

Figure 2. Key nonocular side effects.

Dr. Boyer spoke frankly about the data. “I think you have to realize that, if you had about a 0.7% incidence of stroke in the 0.3-mg arm, then you need to show a 2.5% to 2.6% incidence in the 0.5-mg arm to show statistical significance. That's what a great difference you would need if you had only 1,200 patients. So we didn't have enough patients to really show small differences.”

The next step, therefore, was to look at other randomized clinical ranibizumab studies collectively. Besides the MARINA, ANCHOR and SAILOR trials, the FOCUS and PIER studies were also included in a meta-analysis that showed higher doses of ranibizumab trended toward higher incidences of stroke. However, these results were also not statistically significant and again showed the leading risk factor for the development of stroke was previous stroke.

Dr. Boyer closed with a “wait and see” approach, noting, “We're all anxiously awaiting the CATT trial looking at ranibizumab vs bevacizumab — 1,200 patients — to see whether there's any safety signal with bevacizumab,” he said.

K. BAILEY FREUND ON OPTIMAL DOSING

For nearly as long as retinal physicians have been giving intravitreal injections of anti-VEGF agents, notably Lucentis and Avastin, the question of what is the optimal dosing schedule for these drugs has lingered. In the first of two presentations he gave at the *Retinal Physician* Symposium, K. Bailey Freund, MD, crunched the data from several clinical trials and made some suggestions regarding dosing scheduling.

Dr. Freund, from Vitreous Retina Macula Consultants of New York, began by discussing five ranibizumab trials: HORIZON, SAILOR, PIER, ANCHOR and MARINA. He noted that monthly treatment trials showed sustained improvement in visual acuity for two years; however, he cited data from the PIER and HORIZON studies in which a decline in visual acuity appeared to result from a reduced injection frequency. “We saw a pattern: Once we gave fewer injections, vision started to drop. This drop in vision was presumably explained by recurrent exudation resulting from undertreatment,” he said.

Dr. Freund then turned to phase 2 trials of Regeneron's VEGF Trap-Eye, noting that prn dosing from the initiation of therapy was inferior to a loading sequence of three monthly injections. Dr. Freund said, “So you might ask, 'Well, with those results, why aren't we just treating all patients every month?'” He answered his own question with what

was learned from the PrONTO study: retreatment based on OCT could give visual acuity results comparable to monthly dosing. However, he cautioned, the PrONTO trial was small (37 patients) and not randomized.

Nevertheless, the PrONTO study showed that three injections could dry the macula for an extended period of time. In Dr. Freund's view, monthly dosing may actually be overtreating some eyes. Here Dr. Freund presented his "scorecard," a list of pros and cons of monthly dosing. While, on the one hand, monthly dosing will improve vision by keeping the macula dry and reduce risk of vision loss by reducing the risk of recurrent fluid and hemorrhage, on the other hand, monthly dosing entails greater risks of complications from intravitreal injections, costs more money, is less convenient for patients, and may incur long-term safety concerns.

At this point, Dr. Freund turned briefly towards the possible beneficial effects of monthly dosing on conversion rates from dry to wet in the non-treated fellow eyes (**Figure 3**). Having looked at fellow eyes from the ANCHOR and MARINA trials, Dr. Freund and his colleagues concluded that there was no difference between results for patients receiving monthly ranibizumab versus sham injections. "It doesn't seem that monthly ranibizumab has a prophylactic effect on the fellow eyes with dry disease," he said.

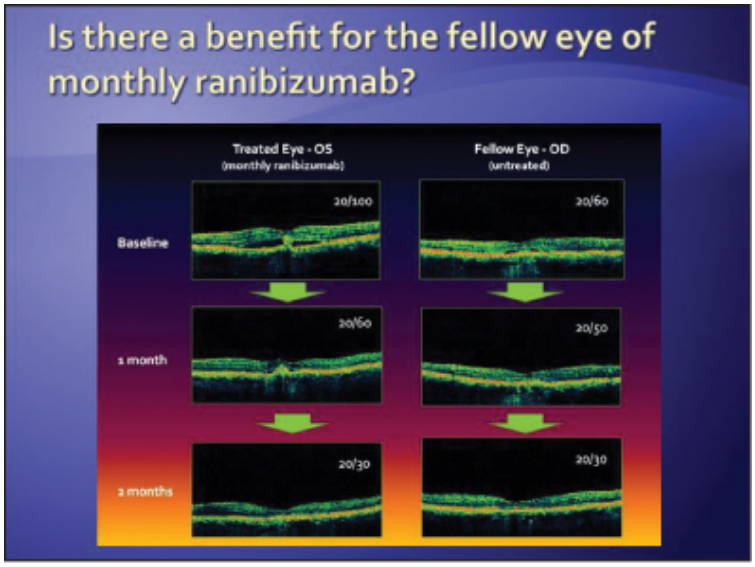

Figure 3. OCT images of fellow eyes in patients treated with ranibizumab.

Conceding further that monthly dosing is often logistically difficult with the population of patients with AMD, Dr. Freund gave his recommendations for which eyes he might consider dosing monthly. These eyes included: those in monocular patients who had lost vision in the fellow eye already due to AMD, those with preserved foveal vision but lesions close to fixation, those that have already demonstrated aggressive recurrent exudation, and those in poorly compliant patients.

Dr. Freund suggested that any optimal dosing schedule will likely need to include at least three initial doses on a monthly basis **(Figure 4)**. Retinal physicians then need to consider several other factors in determining a dosing schedule for each individual patient. An alternative to monthly dosing Dr. Freund discussed at some length was the PrONTO dosing schedule. He provided another "scorecard" here, this one pointing out that the pros were primarily an often reduced number of injections and associated drug cost with theoretically greater systemic safety. The cons included the necessity for monthly visits and OCTs, which are costly and difficult for patients to maintain, and uncertainty regarding when treatments will be administered.

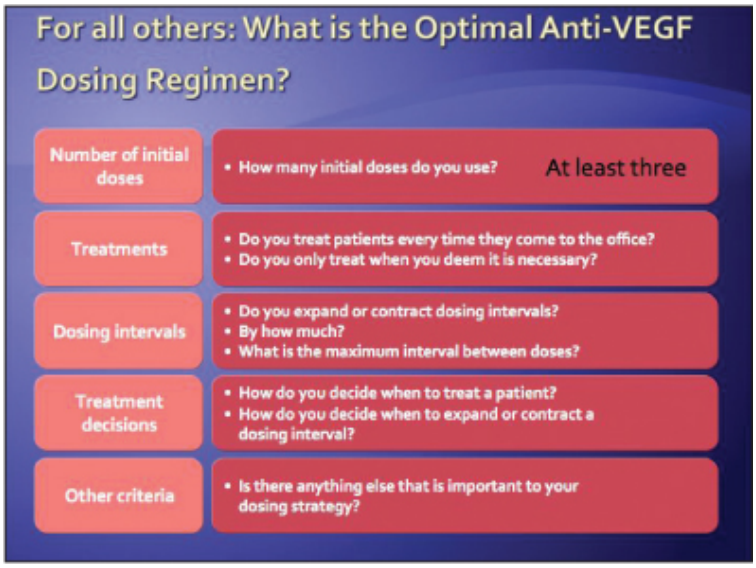

Figure 4. Considerations for optimal dosing of anti-VEGF drugs.

Dr. Freund then showed a few cases from his own practice, noting that recurrent hemorrhage seemed to be a risk with prn dosing. “This raises the question of whether we can completely rely on OCT as an indicator of disease activity,” Dr. Freund said. To demonstrate the correlation between injection frequency and macular hemorrhages, Dr. Freund and his colleagues compared the patients in the ANCHOR, MARINA and PIER studies, concluding that macular hemorrhages occurred in patients more often when dosing was quarterly rather than monthly.

Dr. Freund then described his own “treat and extend” dosing regimen. Monthly injections are given until the macula appears dry on OCT. “And then I just do two simple one- to two-week extensions as long as the OCT, clinical exam and visual acuity remain stable. Patients who do not develop recurrence of exudation at two months will continue on a maintenance regimen with visits and injections every two months,” Dr. Freund said. “With this strategy, you can probably get at least 50% of patients to only six visits and six injections a year,” Dr. Freund noted. He presented a scorecard for treat-and-extend dosing to underscore his points, suggesting that the approach seems to offer a good balance in terms of the goals of maximizing visual outcomes, patient safety and convenience, and minimizing cost to the healthcare system and the burden on retinal physician's practices in terms of managing these cases.

Dr. Freund presented data from a retrospective study conducted in his practice, which found that patients with type 3 neovascularization or RAP lesions managed with the “treat and extend” regimen required, on average, 13 injections and office visits in a period of two years. Visual results in these eyes were similar to those seen in the ANCHOR, MARINA, and PrONTO trials.

He closed his presentation with data on bilateral same-day dosing that showed that these procedures had rates of ocular complications that were similar to what are seen in single-eye injections. He emphasized the notion that optimal dosing is best determined on a case-by-case basis and that there is no “one size fits all” strategy. He said “as retinal specialists we need to combine the available data and our own clinical experience regarding dosing with the specifics of each individual case in order to come up with an optimal dosing strategy tailored to each and every patient.”

DR. FREUND ON LESIONS

Dr. Freund's second presentation was entitled “Does Lesion Composition, Age, or Size Matter?” He began by going over what many consider to be the most important strategies for obtaining the best visual result in treating wet AMD: achieving a dry macula, preventing growth in lesion size, and trying to eliminate the CNV. His focus is

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