

## MONITORING THERAPEUTIC EFFICACY IN THE ANTI-VEGF ERA\*

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ABSTRACT

One of the most important questions with vascular endothelial growth factor (VEGF) inhibitors for age-related macular degeneration is the recommended frequency of monitoring and whether the results of monitoring will guide management decisions. Many clinicians naturally turn to the large, randomized, controlled trials to provide guidance on these questions. However, comparing the results from different clinical trials to ascertain this information can be problematic, as the studies are typically different, in both design and patient populations. This article discusses some of those pitfalls and what the clinical trials reveal about the usefulness of different monitoring methods. Given the uncertainties that remain with optimal dosing and monitoring regimens for anti-VEGF therapies, I propose 2 possible treatment strategies for consideration, described in this article. (*Adv Stud Ophthalmol.* 2007;4(5):127-132)

In studies of vascular endothelial growth factor (VEGF) inhibitors, the most commonly used methods for monitoring efficacy include visual function (acuity, color, contrast, and reading speed), quality of life, biomicroscopy, and imaging, either by fluorescein angiography (FA) or optical coherence tomography (OCT) or both. One of the most important questions with these new treatments is the recommended frequency of monitoring and whether the results of monitoring will guide management decisions. The large, randomized, controlled trials evaluating these new therapies may provide guidance on these questions.

**MONITORING SCHEDULES FROM RANDOMIZED CONTROLLED TRIALS**

In the pegaptanib VEGF Inhibition Study in Ocular Neovascularization, patients' visual function tests and biomicroscopy were performed at least every 6 weeks and FA every 3 months during year 1, and every 6 months during year 2. OCT was performed relatively infrequently, at only a few selected sites, and no analysis was performed of the data (Table).<sup>1,2</sup> For the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration trials of ranibizumab, the monitoring frequencies were slightly different, but similar in overall frequency (Table). One major difference was that quality of life was also measured.<sup>3,4</sup>

The results of these monitoring efforts were used to assess for adverse events, which might have triggered withholding a dose, but, importantly, *these findings were not used to determine whether a randomized study participant should be retreated.* Of note, in the absence

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Table. Monitoring Schedules in the Pivotal Anti-VEGF Clinical Trials

	VISION (pegaptanib)	MARINA, ANCHOR, PIER (ranibizumab)	PrONTO (ranibizumab)	Comments
Vision	Baseline, every 6 weeks	Baseline, every 4 weeks	Baseline, D14, D30, D45, D60, then monthly	Assess for adverse events—dose withholding
Quality of Life	Not performed	Baseline, every 12 months	Not performed	Not used for patient management
Biomicroscopy	Baseline, every 6 weeks	Baseline, every 4 weeks	Baseline, D14, D30, D45, D60, then monthly	Assess for adverse events (eg, uveitis)—dose withholding
Flourescein angiography	Baseline, every 3 months (Year 1), every 6 months (Year 2)	Baseline, every 3 months	Baseline, M1, M2, M3, every 3 months	Assess for adverse events—dose withholding
Optical coherence tomography	Performed at a few selected sites, no analysis	Performed at a few selected sites	Baseline, D1, D2, D4, D7, D14, D30 (after first 2 injections), then monthly	Not used for patient management

ANCHOR = Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PrONTO = Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab; VEGF = vascular endothelial growth factor; VISION = VEGF Inhibition Study in Ocular Neovascularization.

of an adverse event suspected on clinical examination, FA did not reveal any additional adverse events. The presence of choroidal neovascularization (CNV) leakage on FA as well as the presence of fluid on OCT was not related to the treatment frequency. Also, OCT was generally not required and only obtained at a few select sites. Therefore, if one is to follow the clinical trial protocol treatment schedules and the schedules in the drugs' prescribing information, clinical examinations should be performed at all injection visits. Moreover, it appears that FA is unnecessary to follow the drugs' prescribing information once the initial diagnosis of CNV has been made, unless there is suspicion of a relevant adverse event on clinical examination. OCT also appears to be unnecessary to follow the drugs' prescribing information. However, many clinicians most likely are not following this 4- to 6-week mandatory retreatment schedule. Are they undertreating their patients?

#### USING MONITORING RESULTS TO GUIDE DOSING

What do the large, randomized, controlled trials tell us about whether monitoring results can guide dosing? Patients in the PIER study had 3 monthly doses of ranibizumab or sham, followed by quarterly doses. In the MARINA study, dosing was monthly for 24 months. FA and OCT data were collected at some sites, but the data

were not used for retreatment decisions (Table).<sup>3,4</sup>

It is tempting to compare the outcomes from studies, such as PIER and MARINA. Results from the PIER study demonstrated a benefit with ranibizumab compared to sham treatment; however, the visual acuity of ranibizumab-treated patients did not actually improve after 12 months. The observed difference was due to worsening visual acuity for those treated with sham injections (Figure 1). When comparing the MARINA data to the PIER data, the results hint that the PIER treatment protocol may be less effective (Figure 2), as ranibizumab-treated patients in the MARINA study experienced a mean improvement in vision.<sup>4</sup> However, the absolute differences in visual acuity suggest that the 2 treatment schedules may in fact be comparable; both studies show a difference between ranibizumab- and sham-treated groups of approximately 15 to 17 letters after 1 year (Figure 2). There is a danger in comparing the PIER to the MARINA results because the studies were different in important respects. The lack of improvement in the ranibizumab groups in the PIER study may have been due to a patient population with more severe disease having been enrolled in PIER compared to MARINA, although it is important to note the mean visual acuity change from baseline decreased when injections went from monthly to quarterly.

What if the imaging study results were in fact used to guide retreatment decisions; how might this affect outcomes? The Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab (PrONTO) study was a 2-year, open-label study of 40 subjects, designed to measure the efficacy, durability, and safety of a variable dosing regimen of ranibizumab in subjects with neovascular age-related macular degeneration (AMD). In this study, OCT and FA were used as an entry criterion (foveal central subfield [FCS]  $\geq 300 \mu\text{m}$ ) and was based on the automated measurement from the machine. Intravitreal ranibizumab 0.5 mg was administered at baseline, month 1, and month 2, with additional reinjections if there was visual acuity loss of at least 5 letters, with OCT evidence of fluid (defined as subretinal fluid or retinal cysts), an increase in OCT FCS thickness of more than  $100 \mu\text{m}$ , new macular hemorrhage, new classic CNV on FA, or evidence of persistent fluid on OCT 1 month following the previous injection (ie, vision loss was not necessary for retreatment, as long as fluid was persistently detected). Once the fluid disappeared, this criterion no longer was applicable.<sup>5</sup> Monitoring was also more frequent in PrONTO than in the other ranibizumab studies (Table); however, quality of life was not measured.<sup>5</sup>

During the study, the most frequently used criteria for retreatment were vision loss ( $\geq 5$  letters) associated with fluid detection by OCT (31 times) and persistent fluid following last injection (30 times). Increase in central retinal thickness by  $100 \mu\text{m}$  or more and new-onset hemorrhage were each used 12 times, and new classic CNV was used 5 times, as criteria for retreatment. Importantly, reaccumulation of fluid after initial resolution (but which was insufficient to thicken the retina by  $100 \mu\text{m}$  and did not incur vision loss) did not trigger a retreatment.<sup>5</sup>

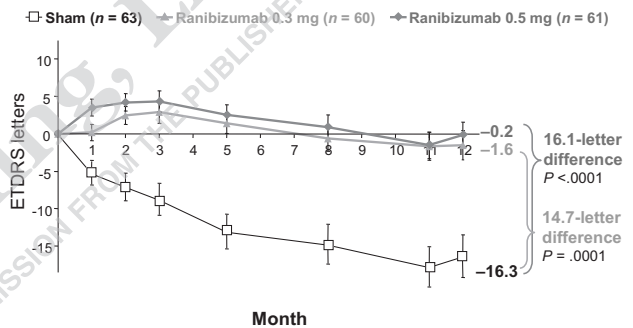
By month 3, only 3 of the 40 eyes enrolled required reinjection based on persistent fluid. Conversely, the number of eyes that did not require retreatment after month 3 was 7, and 8 eyes received only 1 other injection after month 3. In addition, of the 29 eyes with a retinal pigment epithelium (RPE) detachment at baseline, only 14 had resolution by month 3. Therefore, many of these subjects still had pigment epithelial detachments, which were not factored into the retreatment decisions.<sup>5</sup>

By month 12, subjects had received a mean of 5.6

injections (with a possible maximum of 12). The vast majority (95%) avoided moderate vision loss, whereas 35% had moderate visual gain, with a mean of 9.3 letters. The mean reduction in retinal thickness was  $178 \mu\text{m}$ .

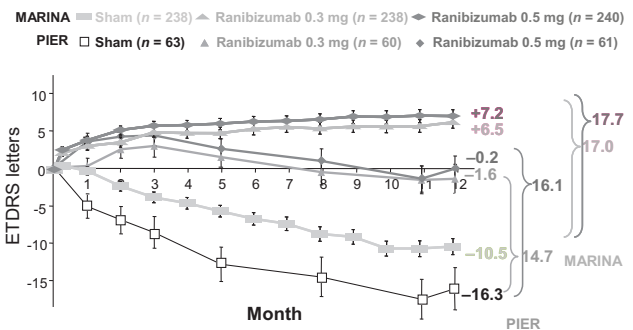
How does the clinician use the PrONTO data? The study results do not show better improvement with the PrONTO than with the PIER dosing regimen. This was a small, open-label study; it is unknown how much better or worse these cases may have done with monthly injections, thus comparisons with other

**Figure 1. Mean Change in Visual Acuity over Time: The PIER Study\***



The mean change in visual acuity from baseline was the primary endpoint. \*Vertical bars are  $\pm$  one standard error of the mean. The primary endpoint is at 12 months. ETDRS = Early Treatment of Diabetic Retinopathy Study.

**Figure 2. Visual Acuity with Ranibizumab Treatment: PIER Versus MARINA**



Although the absolute measures of visual acuity were different between the 2 studies, the absolute difference in visual acuity from baseline was comparable. However, the PIER study group may have had more severe disease. ETDRS = Early Treatment of Diabetic Retinopathy Study; MARINA = Minimally Classic/Occlud Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration.

ranibizumab studies can be misleading. Also, the study investigators note that patients were not retreated unless enough fluid accumulated to increase retinal thickness by 100  $\mu\text{m}$  or if visual function declined. If retreatment was done earlier (eg, when any fluid build-up was observed), would the results with ranibizumab have been more impressive? Unfortunately, the existing data are insufficient to address this question.

The FA results during the follow-up in PrONTO have not been described so far, but important questions remain unanswered. If absence of FA leakage was also used as an endpoint, are the results better? How do the FA results correlate with the OCT findings? How do we manage patients with residual pigment epithelial detachments, but no subretinal fluid or retinal edema? Are there concerns about relying on interpolated, automated, quantitative OCT data? And, can emerging OCT technologies help to answer these questions? We recently showed that errors of retinal boundary detection and thickness measurement occurred in 92% of patients, especially in patients with subretinal pathology.<sup>6</sup> Moreover, we only map 5% of the area with time-domain OCT and interpolate the rest, thus errors in measuring retinal thickness can then be propagated. Also, because only a small area is sampled, we have observed cases in which subretinal fluid is not detected by time-domain OCT, but is identified by a more dense scanning pattern using spectral-domain OCT.

#### PROPOSED TREATMENT PLANS

Given the uncertainties that remain with optimal dosing and monitoring regimens for anti-VEGF therapies, I propose 2 treatment strategies for consideration. The first may be termed the “agnostic plan,” in which the clinician assumes he/she knows nothing beyond the randomized clinical trial data and therefore uses protocols from the pivotal clinical trials to achieve the results shown in those randomized, controlled trials. This translates to patient visits each month for measurement of visual acuity and biomicroscopy to monitor for adverse events or treatment futility, which may prompt withholding treatment. Once the disease appears to be quiescent (eg, for more than 6 months), perhaps the clinician can see the patient a little less frequently. In this treatment strategy, FA and OCT are obtained only as needed (eg, with a clinically suspected adverse event or with unexplained vision loss); they

are not used for retreatment decisions. If the clinician chooses to follow the MARINA protocol, patients will be treated at every visit for 2 years, unless there’s an adverse event or treatment futility. If the clinician chooses to follow the PIER protocol, the patient will be treated monthly for the first 3 months, then quarterly thereafter.

The main pitfall with the agnostic plan is the potential for overtreatment. There are known risks with intravitreal injection, along with patient discomfort and inconvenience. Recent data also suggest possible toxicity with anti-VEGF therapy, albeit at high doses.<sup>7</sup> Finally, some of the cost associated with this treatment could be unnecessary if patients are overtreated.

A second possible strategy may be termed a “tailored approach.” The physician will need to create his/her own tailored approach; I propose one strategy here. All of the studies support monthly injections for at least the first 3 months (eg, phase I of therapy). Thereafter (phase II of therapy), treatment frequency can be tailored based on quiescence, a sample definition of which could be a lesion that is dry (ie, no subretinal fluid, no retinal edema, no or minimal leakage on FA, and no pigment epithelial detachment) for a period of several consecutive months. With this treatment strategy, results from monitoring can be used as follows: if the lesion is not quiescent, continue monthly injections; if the lesion appears to be dry by OCT (defined as the absence of retinal edema, subretinal fluid, or pigment epithelial detachment) and the patient was treated the prior month, repeat FA to confirm absence of leakage before withholding treatment; if the lesion is wet by OCT, then the FA may be deferred unless there are concerns that the apparent fluid is due to chronic cystoid degeneration over a scarred or inactive lesion; and if the lesion is dry on both FA and OCT, hold treatment and follow with monthly OCT until the lesion is quiescent (no activity for 6 months) or fluid recurs (which would trigger retreatment). Once the quiescent stage (ie, phase III of therapy) is reached, the patient does not need to be seen as frequently. Clinical examination would be used to assess for signs of new disease activity (eg, decreased vision, new fluid, lipid, and hemorrhage), in which case additional imaging studies might be warranted (ie, re-entering phase II). Thus, in phase I, monitoring of efficacy is not required for treatment decision making. In phase II, imaging studies are used to assess efficacy and guide retreatment. In phase III, clinical

examination is used to monitor disease activity, with imaging performed as needed.

Some of the disadvantages with the tailored plan include the off-label (ie, unproven) use of these treatments and risk of undertreatment. Thus, when in doubt, I would propose erring on the side of retreatment.

## CONCLUSIONS

Although the pivotal clinical trials of anti-VEGF therapies suggest that retreatments should be performed at regular, prespecified intervals, many clinicians are not performing these treatments at the recommended 4- to 6-week mandatory retreatment schedule. Moreover, the clinical trials do not provide a sound rationale for using FA or OCT findings to monitor efficacy or guide retreatment decisions. The clinician is thus left with 1 of 2 choices: using the trial protocols exactly for both dosing and monitoring in the hopes of achieving outcomes seen in these studies, but at the risk of possible overtreatment, or using information from the studies to synthesize a tailored approach that requires frequent re-evaluation, at the risk of possible undertreatment. Until we learn more about these therapies, I would propose erring on the side of overtreatment, in an effort to more closely adhere to the largest clinical trials.

## Q&A HIGHLIGHTS

### **Question: Is it easier to capture leakage by FA or an OCT change?**

*Dr Sadda:* Certainly, there are concerns that OCT might miss subretinal fluid. The data suggest that FA leakage may still be possible in the absence of fluid on time-domain OCT, but the answer is unclear.

*Dr Bressler:* OCT is fairly good for measuring retinal thickening, for example, in diabetes, or the thickening that occurs overlying the CNV lesion, but it's not great at detecting changes at the RPE choroidal level. And, you can have fibrovascular tissue grow at the RPE choroidal level and not detect that with current OCT technology. We certainly have seen cases in which the OCT is flat, or maybe there's a dry scar, and yet there can be neovascularization at the side of the lesion on fluorescein. Therefore, we don't know if you need OCT or OCT and FA sequentially or none.

Also, FA leaking is hard to evaluate as a lesion is drying up. Is it staining of a neovascular lesion or is it

actually leaking? Fortunately, the benefits of treatment do not depend on FA findings at this time.

### **Question: If you were able to grade leakage, would that be helpful in dosing?**

*Dr Sadda:* We don't have any data to know. As Dr Bressler said, the good news is that we don't have to know because treatment during the clinical trials was not based on that.

*Dr Bressler:* First, we need a good grading system, before we can show that it changes the outcome.

### **Question: If a monocular patient was treated in an "off-label manner" and their vision declined notably, is there any medicolegal issue?**

*Dr Bressler:* I think the answer, in general, would be no. Every day we make clinical decisions based not only on the protocol of a randomized, controlled trial but also on other evidence that is currently available, such as the PrONTO study, which was just a case series, or anecdotal cases. All of that information is evidence. It's not as strong as the randomized clinical trial, but it's evidence. If, based on the totality of that evidence, you concluded for that particular patient, in that condition, that the "off-label" treatment was the best strategy, I don't think there's evidence to show that you have intentionally harmed the patient. Anyone can sue over anything, but I don't think it would be held up by our peers.

### **Question: We talk about early treatment. Do you think there's a role for these treatments in patients who have serous RPEDs?**

*Dr Sadda:* Again, we don't know because we don't have the data.

*Dr Bressler:* Certainly, I am always very suspicious when an angiogram is interpreted in AMD as a serous pigment epithelial detachment because very often there are other features that suggest there's probably fibrovascular tissue contributing to that elevation or detachment of the pigment epithelium. You're rarely going to be off by erring on the side that it's fibrovascular pigment epithelial detachment that is a form of occult neovascularization. There are cases of pure serous pigment epithelial detachment and, if they are not progressing, I would be hesitant to consider ranibizumab therapy for those cases. You can watch them very closely for 3 or 4 weeks and see what happens.

**Question: Are you seeing in your clinics more PIER-like performance or more MARINA-like performance?**

*Dr Sadda:* We're getting a MARINA-like level of response (ie, 30%–40% of the patients are having significant vision improvement).

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