CME SUPPLEMENT TO

RETINA®
THE JOURNAL OF RETINAL AND VITREOUS DISEASES

# REFINING ANTI-VEGF DOSING STRATEGIES

## for Your Patients With Wet AMD

**Based on proceedings from a CME meeting series**

Jointly sponsored by **The New York Eye and Ear Infirmary** and MedEdicus LLC

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**ORIGINAL RELEASE:** February 1, 2013
**LAST REVIEW:** January 14, 2013
**CME EXPIRATION:** February 28, 2014

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

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### CONTENT SOURCE
This continuing medical education (CME) activity captures the proceedings from a CME regional meeting series that was conducted in the fall of 2012.

### ACTIVITY DESCRIPTION
The treatment of neovascular age-related macular degeneration (nAMD) with anti-vascular endothelial growth factor (VEGF) therapy is well established. Important information is emerging from a growing number of studies designed specifically to investigate approaches for optimizing anti-VEGF dosing strategies. This supplement updates clinicians on research findings to enable better patient care.

### TARGET AUDIENCE
This activity intends to educate retina specialists and other ophthalmologists caring for patients with nAMD.

### LEARNING OBJECTIVES
Upon completion of this activity, participants should be better able to:
- Identify the relevant findings of the CATT, VIEW, and HARBOR trials for most appropriate dosing of anti-VEGF therapy for patients with nAMD
- Discuss the ocular and systemic safety aspects of anti-VEGF agents
- Use appropriate dosing regimens and imaging-guided treatment for nAMD in practice

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**Outcomes from clinical trials investigating anti-vascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration (nAMD) led to US Food and Drug Administration approval of ranibizumab and aflibercept for treatment of this condition and widespread use of bevacizumab off-label. Other novel therapies for nAMD are in clinical development, but in the meantime, there has been significant interest in modified anti-VEGF dosing strategies that might reduce the injection and follow-up burden without compromising patient outcomes. Important information is emerging from a growing number of studies designed specifically to investigate approaches for optimizing anti-VEGF dosing strategies. This supplement updates clinicians on research findings to enable better patient care.**

## IMAGING IN nAMD

Diagnostic imaging is an integral tool in the management of nAMD, where it is used to document and confirm the diagnosis, guide therapy choices, and monitor therapeutic response. A standard baseline evaluation includes fundus photography, optical coherence tomography (OCT), and fluorescein angiography (FA). Indocyanine green angiography may also be performed in selected clinical scenarios, such as when it is necessary to differentiate nAMD from central serous chorioretinopathy or when idiopathic polypoidal choroidal vasculopathy is suspected.

Fundus photography is used to document both non-neovascular- and neovascular-related findings, to identify landmarks for laser and photodynamic therapy (PDT), and for following patients with subretinal hemorrhage. OCT has become the primary imaging modality for follow-up of patients with nAMD, however, particularly as clinicians move away from administering anti-VEGF injections on a fixed schedule to one that individualizes the dosing regimen. Most nAMD clinical trials reported to date have used time-domain (TD) OCT for follow-up, but OCT has advanced from the previous TD technology to spectral-domain (SD) platforms that have faster acquisition time and higher resolution. By enabling visualization of more subtle pathology, SD-OCT imaging may offer more insight about exudation activity. However, definitions and treatment criteria based on SD-OCT are still evolving.

## OPTIMIZING MANAGEMENT OF nAMD WITH VEGF INHIBITORS

Current treatment of nAMD involves the use of VEGF blockers to control exudation, and it is obvious to clinicians using any of the available drugs that these agents are rapidly effective in most patients. Their use in clinical practice, however, should be guided by the results of randomized controlled clinical trials and other published clinical study evidence.

The efficacy of ranibizumab in the treatment of nAMD was established in the phase 3 MARINA and ANCHOR studies.[1,2] In these trials, patients receiving fixed monthly injections of ranibizumab 0.5 mg achieved on average a 7- to 11-letter gain

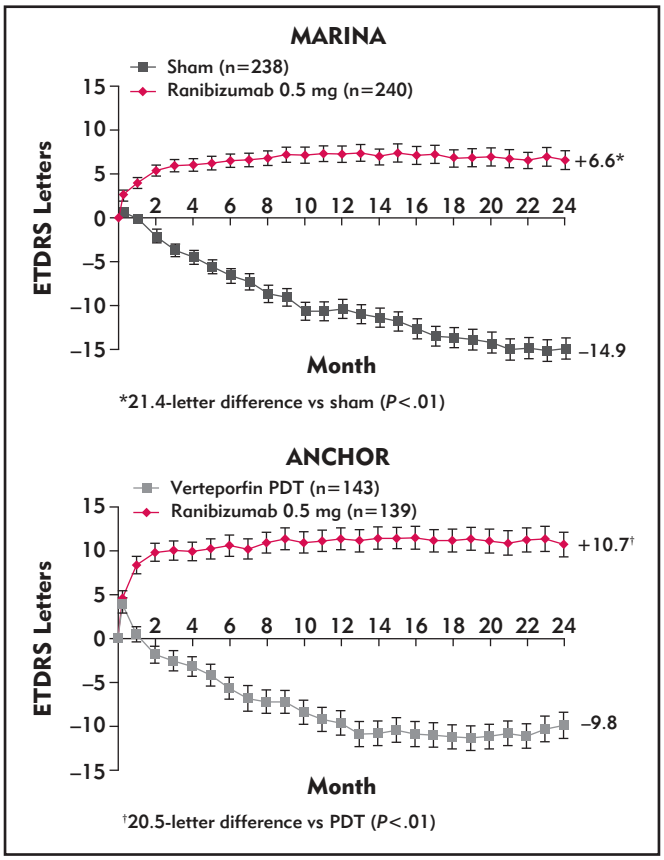


FIGURE 1. Ranibizumab phase 3 trial results.[1,2]

from baseline ETDRS visual acuity (VA) that was maintained over 2 years (FIGURE 1); 33% to 40% of patients gained 3 or more lines from baseline VA. With their broad enrollment criteria, the MARINA and ANCHOR patient populations were fairly representative of the typical nAMD patients seen in daily practice, and the unprecedented functional outcomes achieved with monthly ranibizumab in these studies became a reference standard for comparing new treatments and dosing strategies.

### Fixed quarterly injections

A fixed quarterly injection schedule after an initiation/induction phase with 3 monthly doses was the first deviation from monthly treatment investigated for ranibizumab. It was studied first in the PIER trial in which patients were randomized to receive ranibizumab 0.3 mg, ranibizumab 0.5 mg, or sham, all using the quarterly maintenance dosing scheme.[3,4] Patients in the active treatment arms achieved rapid and significant improvement in VA during the initiation phase, but VA began to decline thereafter, falling to just below baseline at 12 months, and remaining below baseline through month 24.

Fixed quarterly dosing was also investigated in the more recent EXCITE study that randomized patients to quarterly dosing with ranibizumab 0.3 or 0.5 mg or to a control group receiving monthly ranibizumab 0.3 mg.[5] Outcomes for the quarterly dosing arms in EXCITE were better than those in PIER, with patients maintaining a mean gain from baseline VA of 4 to 5 letters at 12 months. But the treatment benefit was superior in the control patients who received monthly injections; their mean VA gain was 8.3 letters.

While it was clear from PIER and EXCITE that results using quarterly ranibizumab injections are not as good as those using monthly dosing, there were patients in each trial who did very well on the reduced dosing schedule, supporting the idea that some individuals can have good outcomes receiving less than monthly injections.

## Individualized dosing strategies

Currently, individualization of anti-VEGF dosing schedules is the norm in clinical practice, with an aim to maintain a dry macula, because achieving this end point appears to correspond with the best VA results. Treatment begins with an initiation period to eliminate all signs of macular exudation and then is continued with a maintenance phase that is based on either a treat-and-observe ("PRN") or a treat-and-extend (TAE) approach. With PRN treatment, patients return for follow-up at fixed intervals, but are retreated only for signs of recurrent exudation. In TAE, patients are treated monthly until the macula is dry, and then the interval between treatments is extended by fixed increments (eg, 2 weeks) until a maximum intervisit interval is reached.

Although there are more published data on outcomes with PRN than for TAE dosing, results from a 2012 American Society of Retina Specialists member survey show that retina specialists in the United States and Canada favor the TAE approach over PRN by nearly 3:1.[6] According to data from a Medicare claims analysis, however, which showed that nAMD patients received an average of just 4.3 anti-VEGF injections in their first year of therapy, it appears that many patients are being undertreated.[7]

## PRN trials

PrONTO was the first prospective study to investigate PRN anti-VEGF treatment of nAMD.[8] This open-label study enrolled 40 patients who received ranibizumab 0.5 mg for 3 consecutive monthly injections and were then followed monthly to determine the need for retreatment. On average, VA increased after 3 months by a mean of approximately 2 lines and was maintained at that level through 2 years, with patients receiving an average of 5.6 injections in year 1 and 4.3 injections in year 2.

SAILOR, started in 2005, was the first large, industry-sponsored study to investigate PRN treatment with ranibizumab.[9] Outcomes were not as good as in PrONTO, and that has been attributed to use of less frequent follow-up and less stringent retreatment criteria in SAILOR, criteria that would be considered inadequate by today's standards. In the first year of SAILOR, patients received an average of only 4.9 injections and had 9 office visits, and mean VA declined continuously after patients completed the 3-dose initiation phase **(FIGURE 2)**.

The European SUSTAIN study used the same retreatment criteria as SAILOR, but followed patients every month.[10] During the first year, the mean number of treatments per patient was 5.6, which was higher than in SAILOR and corresponded with better 1-year VA results. While VA improvement still peaked at month 3, patients had a mean gain of about 4 letters at 1 year.

The CATT study was the first large randomized trial comparing bevacizumab and ranibizumab, and it also compared fixed monthly and PRN dosing for both drugs.[11,12] There was no initiation phase for the PRN patients, but they were followed monthly and retreated with zero tolerance for any fluid on OCT

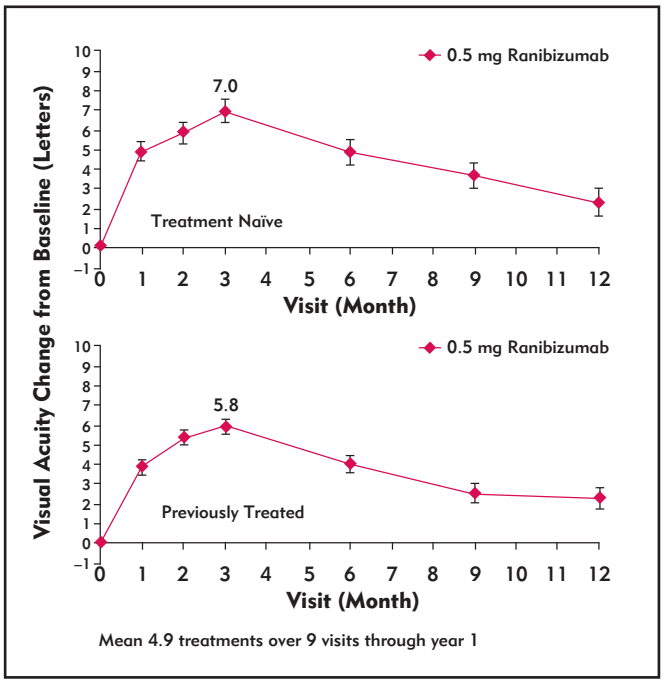


**FIGURE 2.** SAILOR: Mean change in VA (letters) over time.[9]

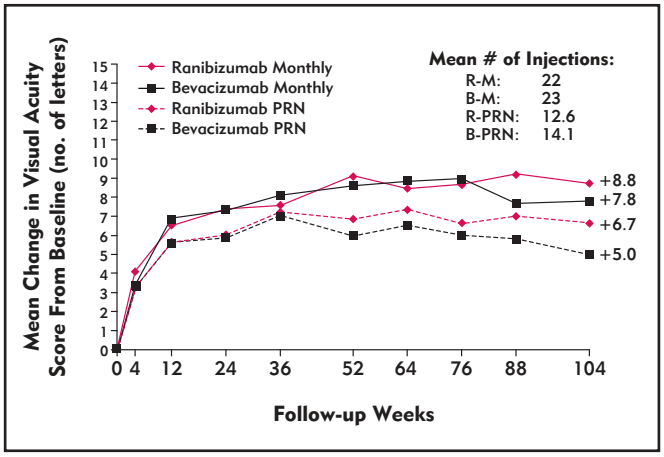


**FIGURE 3.** CATT 2-year outcomes.[12]

or other evidence of choroidal neovascularization (CNV) activity. In addition, patients in the fixed arms were re-randomized at 1 year to continue monthly dosing or to be switched to PRN dosing.

At 1 year, bevacizumab and ranibizumab demonstrated essentially equivalent effects for improving VA when the 2 drugs were compared using the same dosing regimen. However, the mean gain from baseline VA was approximately 2 letters lower in the PRN arms than in the corresponding monthly treatment groups. The 1-year data also dispelled the concept that bevacizumab has a longer duration of action than does ranibizumab because the average number of treatments administered was slightly higher in the bevacizumab PRN arm than in the ranibizumab PRN group (7.7 vs 6.9). After 2 years, bevacizumab again proved to be noninferior to ranibizumab, but there was a statistically significant difference favoring monthly injection over PRN treatment for a greater mean gain from baseline VA ($P$=.046) **(FIGURE 3)**. Patients who crossed

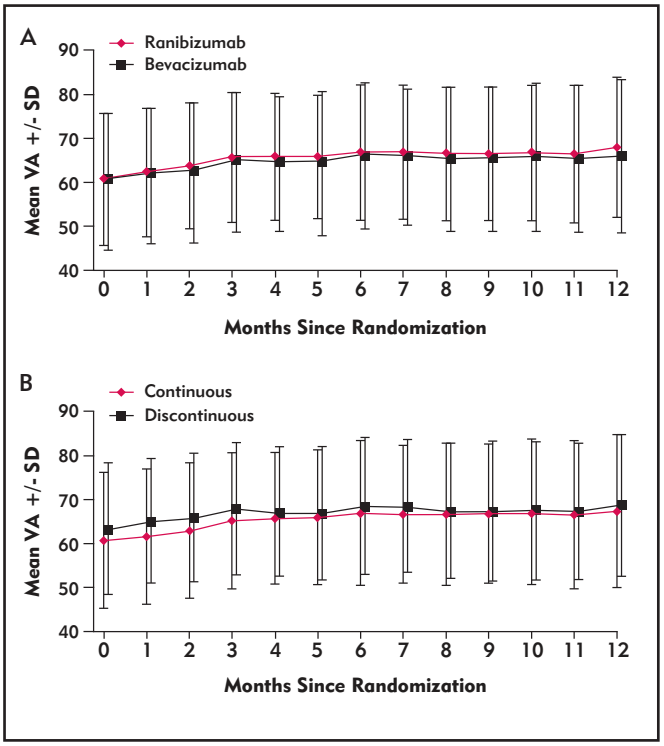


FIGURE 4. IVAN: Mean best corrected visual acuity (BCVA) through 1 year analyzed by medication arm (A) and by treatment regimen (B)[13]
SD=standard deviation.

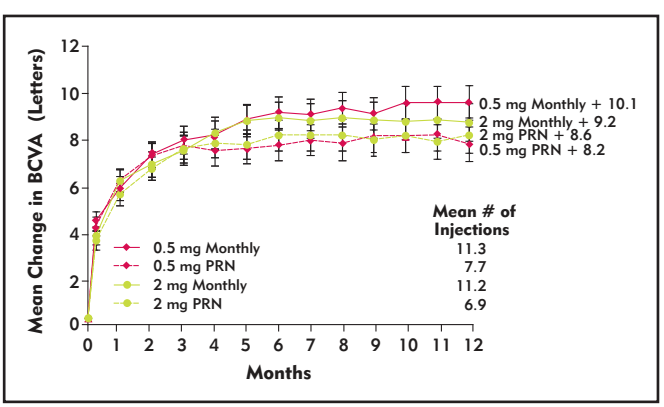


FIGURE 5. HARBOR mean change in BCVA.[14]

over from fixed monthly to PRN dosing had an average VA loss of 2.2 letters between 12 and 24 months, and their final VA outcome was no different from that in patients who received PRN dosing from the outset of the study.

Monthly and PRN bevacizumab and ranibizumab were also investigated in the prospective, randomized, 2-year IVAN trial conducted in the United Kingdom.[13] A graphic display of mean change in VA over time during the first year of the study shows nearly superimposable lines for the pooled ranibizumab and pooled bevacizumab groups as well as for the pooled PRN ("discontinuous") and pooled monthly ("continuous") dosing groups (FIGURE 4). The 2-year data from IVAN are not yet available.

HARBOR, which is the first study of anti-VEGF treatment for nAMD using SD-OCT, was designed to evaluate different doses of ranibizumab—0.5 and 2.0 mg—each administered monthly or PRN after 3 loading doses.[14] In HARBOR, mean VA improvement was approximately 2 letters better in the monthly vs PRN ranibizumab 0.5-mg group, 10.1 vs 8.2 letters, and there was no benefit of the higher dose of ranibizumab for improving the VA outcome or reducing the number of injections needed in PRN dosing (FIGURE 5). Another important finding from HARBOR, which corroborates data from MARINA and ANCHOR, is that treating disease earlier translates into better outcomes. Analyses to identify factors predicting VA outcomes showed that the smaller the CNV lesion at baseline, the better the vision improvement at 12 months.[15]

Prior to the reports from CATT and IVAN, published data on PRN bevacizumab was available only from the ABC trial, a prospective randomized study comparing bevacizumab against the prior standard of care (pegaptanib, verteporfin PDT, or observation).[16] Patients in the bevacizumab group received 3 consecutive injections at 6-week intervals and then were retreated if they had persistent or recurrent subretinal fluid, new hemorrhage, new classic CNV, or VA loss of ≥5 letters with new intraretinal fuid. After 12 months, the bevacizumab patients had received a mean of 7 treatments out of a possible 9; they had a mean VA gain of 7 letters, and 32% of patients gained ≥3 lines. In terms of both vision improvement and number of treatments, the results were similar to those in the PRN bevacizumab arm during the first year of CATT.

## TAE trials

There is strong rationale for the TAE approach, but so far, published data on its efficacy exist only from retrospective analyses. One such study evaluated data from 92 consecutive patients treated over an 18-month period at Wills Eye Hospital, Philadelphia, Pennsylvania.[17] VA outcomes comparable to those in MARINA and ANCHOR were achieved, but with fewer injections. Mean VA improved from 20/135 at baseline to 20/77 at 1 year, 96% of eyes lost <3 Snellen lines of VA, and 32% of eyes gained 3 or more lines. The average number of injections was 8.4 in the first year and approximately 7.5 in the second year.

Oubraham and colleagues also published a retrospective analysis of ranibizumab-treated patients managed with a TAE regimen and compared the outcomes with a historic control group of patients who had been treated with a PRN approach.[18] The 1-year VA results favored TAE over PRN with mean gains in the 2 groups of 10.8 and 2.3 letters, respectively. The mean number of treatments was higher for the TAE than for the PRN approach, 7.8 vs 5.2, but the mean number of follow-up visits for TAE was similar to that of the PRN group, 8.5 vs 8.8, and less than for a PRN approach that required monthly follow-up visits.

Data from a retrospective case series of 74 eyes with new onset nAMD treated at Wills Eye Hospital with a TAE approach using bevacizumab showed results that were similar to the MARINA and ANCHOR trials in terms of VA outcomes at 1 year, but this benefit was achieved with a mean of only 8 treatments.[19]

## Dosing aflibercept

The efficacy of aflibercept for treatment of nAMD was established in the VIEW 1 and VIEW 2 studies that evaluated aflibercept 2 mg every 8 weeks (given after a loading dose of 3 monthly injections)

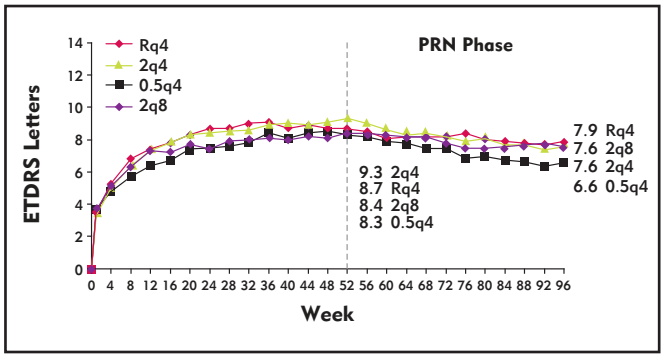


FIGURE 6. VIEW—2 years: mean change in VA.[20,21]

Rq4=ranibizumab 0.5 mg monthly; 2q4=aflibercept 2 mg monthly; 0.5q4=aflibercept 0.5 mg monthly; 2q8=aflibercept 2 mg every 2 months after 3 initial monthly doses.

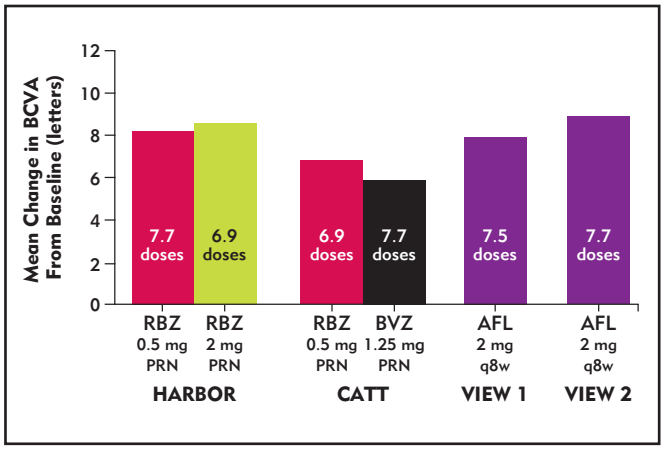


FIGURE 7. Mean number of anti-VEGF injections per year in nonmonthly dosing arms receiving monthly follow-up.[11,12,15,20]

AFL=aflibercept; BVZ=bevacizumab; RBZ=ranibizumab.

as well as monthly aflibercept 2 mg or 0.5 mg.[20] A control group received ranibizumab 0.5 mg monthly.

VA improvements were similar across all 4 arms during the first 52 weeks and all aflibercept regimens were noninferior to ranibizumab in the primary end point analysis of proportion of eyes maintaining vision (≤3 lines of loss) at 52 weeks (FIGURE 6).[20] Based on these results, aflibercept was approved at the 2-mg dose for administration every 8 weeks after 3 consecutive monthly injections.[20] The VIEW trials design, however, did not include an arm with ranibizumab every other month, so we do not know how patients treated in that fashion would have performed. These data show that, on average, dosing aflibercept by the label should yield results that are as good as monthly dosing. In some patients, however, more frequent dosing may be needed to get the desired stabilizing effect.

In the second year of the VIEW studies, all treatment arms were switched to PRN dosing using their originally assigned drug. Patients were evaluated monthly and retreated based on older retreatment criteria of a VA loss of ≥5 letters from the best previous score or a ≥100-micron increase in central retinal thickness compared with the lowest previous value. There was also a provision to retreat if there was any new or persistent edema on OCT; and so, as in CATT, there was zero tolerance for any fluid. However, the PRN regimen was also "capped" so that all patients were retreated at least every 3 months.

Results from follow-up to 96 weeks showed all 4 treatment arms did well (FIGURE 6).[21] All groups had a slight decrease in mean VA compared with 1 year (-0.8 to -1.7 letters), but compared with baseline, mean VA was increased by between 6.6 and 7.9 letters. Mean number of treatments from weeks 52 to 96 were 4.1 and 4.2 in the aflibercept 2 mg-every-4-weeks and 2 mg-every-8-weeks groups, respectively, and 4.7 in the ranibizumab group. Per the capped PRN design, all patients would have received a minimum of 4 injections. These data suggest aflibercept 2 mg may have longer-lasting efficacy than ranibizumab, but the difference between them is relatively small.

## ANTI-VEGF SAFETY

The ocular safety and tolerability of intravitreal injection of anti-VEGF agents has been remarkable. Infection is the most commonly reported serious adverse event, but it is related to the route of administration and not the medication. In studies with at least 2 years of follow-up, there are no reports of ocular adverse events associated with VEGF inhibition, such as thrombotic events in the retinal vasculature. Additionally, inflammatory events are rare and occur at a lower rate than might be predicted considering that these treatments introduce a foreign protein into the eye.

Intravitreal anti-VEGF treatments also appear to be safe from a systemic standpoint. While the estimated intravitreal half-lives of the 3 anti-VEGF agents are similar,[22] there are data showing that the serum half-lives of aflibercept and bevacizumab are longer than that of ranibizumab,[23,24,25] and safety data from IVAN showed greater systemic VEGF inhibition with bevacizumab compared with ranibizumab.[13] Further study and data from larger patient populations are needed, however, to understand the systemic safety profile of intravitreal anti-VEGF treatment and to determine if there are differences between the drugs. In practice, clinicians need to keep in mind that a potential for systemic anti-VEGF inhibition exists, and it might be prudent to exert more caution when treating high-risk patients.

## SUMMARY OF THE EVIDENCE

The fact that nAMD is a heterogeneous disease supports the practice of individualizing anti-VEGF therapy. Currently, the goal of treatment is to maintain a dry macula, and that can be achieved using various dosing regimens. A fixed monthly injection approach for an indefinite timeframe is probably overtreatment for many patients. The best nonmonthly regimen is unknown, but from available data, it is clear that visual outcomes are better when patients receive close follow-up and more treatments. Based on data from the PRN groups in the HARBOR and CATT studies, the aflibercept 2 mg-every-8-weeks treatment arm in the VIEW studies, and retrospective analyses of experience with TAE at Wills Eye Hospital, it appears that regardless of the anti-VEGF agent used, patients need to receive an average of 7 to 8 injections over the course of the first year to match the VA gains achieved with fixed monthly dosing (FIGURE 7).[11,12,15,20] What is not yet known is whether it might be possible to reach the same outcomes with fewer injections using aflibercept on a PRN or TAE schedule.

## THE FUTURE

A number of other questions regarding anti-VEGF dosing for treatment of nAMD remain unanswered. Whether or not an induction phase is needed is unclear. While an induction phase is currently usual practice, based on CATT, it may not be essential, especially if anti-VEGF therapy is started early in the course of neovascular disease.

The optimum approach to TAE also is unknown in terms of the best length for the extension intervals, the maximum duration of the intervisit interval, and how to rechallenge a patient who has experienced a recurrence. There also are issues to be resolved about long-term use of anti-VEGF treatment, including the relative efficacy and safety of the different agents, how anti-VEGF treatment affects the development of geographic atrophy, what risk of intraocular pressure elevation exists with repeated injections, and whether tolerance or tachyphylaxis occurs over time. Further insights on modifications in anti-VEGF dosing strategies will be forthcoming with the release of new study data. Results from the second year of HARBOR are anticipated in early 2013, and a prospective pilot study investigating a TAE regimen with aflibercept is being undertaken at Wills Eye Hospital. In Norway, the LUCAS study is investigating a TAE approach comparing bevacizumab and ranibizumab.

## CASE STUDIES FROM WILLS EYE HOSPITAL

**Carl D. Regillo, MD**

### Case 1

A patient presented with new onset nAMD with best corrected visual acuity (BCVA) of 20/200, occult leakage centrally on FA, and central subfield thickness (CST) of 465 microns on OCT. The patient was given an educational brochure describing the 3 anti-VEGF treatments available and explaining that based on current evidence, they appear to be comparably safe and likely to provide a good result.

Treatment was started with ranibizumab 0.5 mg monthly. VA and CST improved, reaching 20/40 and 172 microns, respectively, at the third injection. At the fourth visit, VA was 20/30 and CST was 219 microns, but the patient refused further treatment and did not return for another 2 months with VA of 20/400 and CST of 501 microns. Ranibizumab was given, and after 1 month VA was 20/50 and CST 163 microns. Ranibizumab was given again, and at the next visit, approximately 6 weeks later, VA was 20/80 and CST 316 microns.

The yo-yo–like response in this and similar cases led me in the direction of the TAE approach, which is a more continuous style of therapy. When there is recurrent edema in nAMD, there also may be growth of neovascularization, and complete vision recovery may not be possible with significant growth of the neovascular complex. The PRN approach, with its inherent multiple recurrences of edema, is more likely to lead to nonrecoverable setbacks than is the TAE approach, which is a continuous form of treatment.

### Case 2

This case demonstrates successful TAE rechallenge/re-extension. The patient presented with nAMD with occult neovascularization, BCVA of 20/100, pigment epithelial detachment, subretinal fluid, and macular edema. After 2 monthly injections of ranibizumab, BCVA improved to 20/40 and OCT demonstrated no signs of exudation.

The patient was converted to a TAE regimen using a 2-week extension interval. At 6 weeks after the last injection, BCVA was 20/25 and the patient was treated. Eight weeks later, VA was 20/30, the macula was dry, and another injection was given. When the patient returned after 10 weeks, exudation had recurred. The patient received the injection and the follow-up interval was reduced to 8 weeks. The disease was still under control when the patient returned, another injection was given, and the patient was instructed to return in 10 weeks. At that visit, BCVA was 20/30, the OCT looked good, and the follow-up was further extended to 12 weeks.

Currently, when patients have recurrent exudation, I am less likely to rechallenge them so soon with re-extension. However, this particular patient continued to do well on an interval that was successfully lengthened to 3 months and has been maintained that way for an additional 2 years.

### Case 3

This case presents a patient who was managed successfully with ranibizumab TAE to 8 weeks, experienced recurrence with a 10-week extension interval, and was kept on an 8-week interval without rechallenge. At baseline, VA was 20/400 and CST was 516 microns. At 4 weeks after an initial ranibizumab injection, VA was 20/100 and CST was 282 microns. A second injection was given and then a third 4 weeks later when VA had improved to 20/40 and CST to 198 microns. After the treatment interval was eventually increased to 10 weeks, VA worsened to 20/60 and CST to 312 microns. Ranibizumab was administered and the patient was told to return at 8 weeks. VA and CST improved and the patient was maintained with an 8-week injection interval. The decision was made not to rechallenge this patient by extending the treatment interval again because of poor vision in the fellow eye.

### Case 4

This case illustrates use of aflibercept as an alternative in a patient who became refractory to ranibizumab. The patient was receiving monthly ranibizumab for nAMD OD and had treatment initiated OS after 2 years. One year later, VA was 20/40 OS, but worsened from 20/80 to 20/200 OD with recurrence of macular exudation. The decision was made to switch to aflibercept bilaterally. VA was unchanged OU, but all signs of exudation resolved OD (FIGURE 8). A TAE approach was started and both eyes remained dry when the treatment interval was extended to 5 weeks, but extension to 6 weeks was unsuccessful. The patient was maintained successfully on aflibercept injections every 5 weeks.

The question of whether tolerance or tachyphylaxis develops to anti-VEGF therapy remains unanswered, but there is emerging evidence suggesting that it is a real phenomenon and that switching to another anti-VEGF agent may be helpful. A

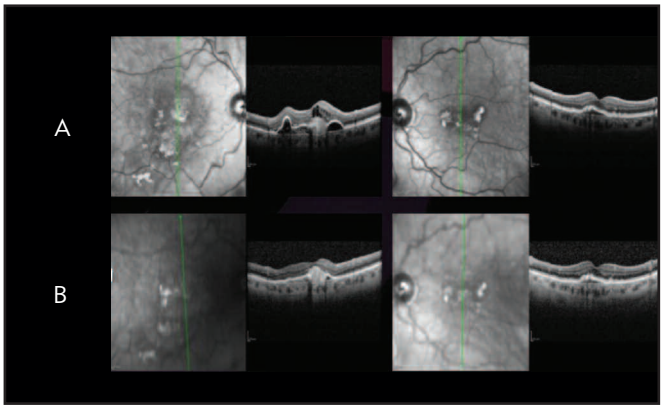


**FIGURE 8.** OCT for patient in Case 4 at presentation 4 weeks after last monthly ranibizumab injection (A) and 4 weeks later after receiving aflibercept (B).

*Photo Courtesy of Carl D. Regillo, MD*

retrospective study including approximately 1000 patients having at least 12 months of follow-up reported a 2% rate of tachyphylaxis, defined as lack of response to retreatment at the time of reactivation of CNV in patients having responded to initial treatment.[26] A second retrospective study included eyes that developed tachyphylaxis to ranibizumab or to bevacizumab and were then switched to the alternate agent. Of the 26 eyes in the analysis, approximately 80% had at least some response using the other drug.[27]

I recently had a patient much like those in the study described above. The patient was receiving bevacizumab every 4 weeks for 2 years. I switched the patient to ranibizumab and 1 month later the OCT was dramatically better with some limited visual improvement. Switching, especially if a patient has been on long-term therapy, does seem to help some patients to at least dry their macula. Maybe that will translate into slowing vision loss or preventing further vision loss.

## ANSWERS TO SOME COMMONLY ASKED QUESTIONS

**QUESTION:** How often do you find that patients being treated with aflibercept once every 8 weeks show evidence of reactivation and need more frequent injections?

**ANSWER:** Although the product information for aflibercept states that additional efficacy was not observed in the pivotal trials when the 2-mg dose was injected monthly compared with administration every 2 months,[23] there are some patients who may need more frequent injections to maintain disease control. Currently, it is too early to know how often that occurs, especially because patients being treated with aflibercept are often difficult cases with aggressive disease who have either not responded adequately to monthly ranibizumab or bevacizumab or who cannot have the treatment interval extended past 4 weeks when trialed with a TAE approach.

**QUESTION:** Very occasionally, clinicians encounter patients who remain completely dry for 1 to 2 years after receiving just 2 or 3 monthly injections of bevacizumab or ranibizumab. Is there any explanation for these responders, or any feature that can be used to identify them a priori?

**ANSWER:** There are no known baseline characteristics for predicting a prolonged response to anti-VEGF therapy. However, current treatment strategies are based on the notion of continuous treatment. Additionally, many clinicians have likely had experience in the past wherein they stopped treatment in a patient who was doing well, only to have that individual return several months later with a significant setback. Therefore, except in an end-stage scenario or if the diagnosis of nAMD is in doubt, do not stop anti-VEGF therapy.

From a long-term perspective, another issue to consider is that even though the nAMD may be well controlled, vision loss can occur over time because of the development of geographic atrophy. In the second year of CATT, rates of geographic atrophy were higher in the monthly arms than in the PRN dosing arms,[12] which led to the idea that continuous, frequent anti-VEGF treatment might be promoting atrophy. Although theoretically possible, that remains to be proven. Nevertheless, it is clear that achieving consistently good long-term results for nAMD patients will require therapies addressing both the wet and dry components of the disease.

**ABC**=[Avastin] Bevacizumab for Choroidal Neovascular Age-Related Macular Degeneration

**ANCHOR**=Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration

**CATT**=Comparison of AMD Treatment Trials

**ETDRS**=Early Treatment Diabetic Retinopathy Study

**EXCITE**=Efficacy and Safety of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration

**HARBOR**=Study of Ranibizumab Administered Monthly or on an As-Needed Basis in Patients With Subfoveal Neovascular Age-Related Macular Degeneration

**IVAN**=Inhibit VEGF in Age-Related Choroidal Neovascularization

**LUCAS**=LUcentis Compared to Avastin Study

**MARINA**=Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration

**PIER**=Randomised, Double-Masked, Sham-Controlled, 2-Year Study Designed to Assess the Safety and Efficacy of Ranibizumab in Patients With Neovascular (Wet) Age-Related Macular Degeneration (With or Without Choroidal Neovascularisation)

**PrONTO**=Prospective Optical Coherence Tomography Imaging of Patients With Neovascular AMD Treated With Intra-Ocular Ranibizumab

**SAILOR**=Safety Assessment of Intravitreal Lucentis® for Age-Related Macular Degeneration

**SUSTAIN**=Study of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration

**VIEW 1** [North America], **VIEW 2** [International]=VEGF Trap-Eye Investigation of Efficacy and Safety in Wet AMD

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# CME POST TEST QUESTIONS

To obtain *AMA PRA Category 1 Credit™* for this activity, you must complete the CME Post Test online at http://www.MedEdicus.com, Educational Activities tab, and click the Post-Test & CME Certificate button. Alternatively, you can complete the CME Post Test by writing the best answer to each question in the Answer Box located on the Activity Evaluation/Credit Request form on the following page.

See detailed instructions at **To Obtain *AMA PRA Category 1 Credit™*** at page 2.

1. Studies investigating fixed quarterly injections of ranibizumab:
   A. showed 1-year VA outcomes comparable to those of MARINA and ANCHOR only when using a 2-mg dose
   B. consistently showed mean VA gains of 4 to 5 letters at 1 year
   C. had poor outcomes because they did not include an induction phase
   D. showed mean peak VA improvements at 3 months with visual decline thereafter

2. A TAE approach to ranibizumab dosing is:
   A. supported by results of prospective randomized studies
   B. favored over monthly dosing among US and Canadian retina specialists by almost 3:1
   C. associated with 1-year VA outcomes comparable to those of MARINA and ANCHOR, according to a retrospective study
   D. superior to PRN aflibercept, according to the VIEW studies

3. SD-OCT imaging:
   A. was used to assess anatomic end points in MARINA and ANCHOR
   B. is the new standard for OCT follow-up because it reveals more subtle pathology
   C. has higher resolution than TD-OCT
   D. has a longer acquisition time than does TD-OCT

4. HARBOR:
   A. compared ranibizumab and bevacizumab PRN
   B. showed no benefit for ranibizumab 2 mg vs 0.5 mg
   C. showed similar VA outcomes at 1 year in groups treated monthly or PRN
   D. is the first nAMD study to use swept-source OCT

5. The PRN arms in CATT had:
   A. more systemic VEGF inhibition than the monthly arms
   B. worse 2-year VA results than the monthly arms because of higher rates of geographic atrophy
   C. better outcomes with bevacizumab than with ranibizumab, possibly because of the use of more injections
   D. similar VA outcomes whether PRN treatment was initiated at entry or after 1 year of monthly dosing

6. Aflibercept 2 mg for treatment of nAMD:
   A. was associated with better VA outcomes than ranibizumab 0.5 mg when both were dosed monthly
   B. is recommended to be administered every 8 weeks without any induction phase
   C. appears to cause higher rates of systemic adverse events than does ranibizumab because of its longer half-life
   D. lacks data on dosing in a TAE regimen

7. Which of the following statements is consistent with published reports of tachyphylaxis in patients receiving anti-VEGF therapy for nAMD?
   A. Tachyphylaxis affected 2% of 1000 patients treated with ranibizumab for at least 12 months
   B. Tachyphylaxis responded to increased frequency of anti-VEGF injections in approximately 80% of patients
   C. Tachyphylaxis occurs faster and at a higher rate with PRN vs TAE treatment
   D. Tachyphylaxis usually represents a misdiagnosis in patients whose vision loss is unrelated to nAMD

8. The most commonly reported serious ocular adverse event associated with anti-VEGF treatment for nAMD is:
   A. vitreous hemorrhage
   B. glaucoma
   C. infection
   D. retinal vascular thrombotic events

9. Which of the following statements is true regarding the systemic safety of intravitreal anti-VEGF treatment for nAMD?
   A. Bevacizumab is safer than ranibizumab
   B. Aflibercept is safer than bevacizumab and ranibizumab
   C. There are no systemic safety concerns
   D. It might be prudent to exert more caution in high-risk patients

10. Based on available evidence from studies of nonmonthly anti-VEGF treatment for nAMD, it appears patients should receive a minimum of ____ injections during the first year of treatment to match the VA gains achieved with monthly dosing.
    A. 9 to 10
    B. 8 to 9
    C. 7 to 8
    D. 6 to 7

# ACTIVITY EVALUATION/CREDIT REQUEST

## Refining Anti-VEGF Dosing Strategies for Your Patients With Wet AMD

**ORIGINAL RELEASE:** February 1, 2013
**LAST REVIEW:** January 14, 2013
**CME EXPIRATION:** February 28, 2014

To receive *AMA PRA Category 1 Credit*™, you must complete this **Evaluation** form and the **Post Test**. Record your answers to the **Post Test** in the **Answer Box** located below. Mail or Fax this completed page to **The New York Eye and Ear Infirmary**–ICME, 310 East 14th Street, New York, NY 10003 (Fax: 212-353-5703). Your comments help us to determine the extent to which this educational activity has met its stated objectives, assess future educational needs, and create timely and pertinent future activities. Please provide all the requested information below. This ensures that your certificate is filled out correctly and is mailed to the proper address. It also enables us to contact you about future CME activities. Please print clearly or type. Illegible submissions cannot be processed.

**PARTICIPANT INFORMATION** (Please Print) ❑ Home ❑ Office

Last Name _____ First Name _____

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**Please note: We do not sell or share e-mail addresses.** *They are used strictly for conducting post-activity follow-up surveys to assess the impact of this educational activity on your practice.*

**Learner Disclosure:** To ensure compliance with the US Centers for Medicare and Medicaid Services regarding gifts to physicians, **The New York Eye and Ear Infirmary** Institute for CME requires that you disclose whether or not you have any financial, referral, and/or other relationship with our institution. **CME certificates cannot be awarded unless you answer this question.** For additional information, please call NYEE ICME at 212-979-4383. Thank you.

❑ Yes ❑ No I and/or my family member have a financial relationship with **The New York Eye and Ear Infirmary** and/or refer Medicare/Medicaid patients to it.

❑ **I certify that I have participated in the entire activity and claim 1.5 *AMA PRA Category 1 Credits*™.**

**Signature Required** _____ **Date Completed** _____

**OUTCOMES MEASUREMENT**

❑ Yes ❑ No **Did you perceive any commercial bias in any part of this activity? IMPORTANT! If you answered "Yes," we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

_____

**Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:**
**5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree**

Upon completion of this activity, I am better able to:

| | | | | | |
|---|---|---|---|---|---|
| • Identify the relevant findings of the CATT, VIEW, and HARBOR trials for most appropriate dosing of anti-VEGF therapy for patients with nAMD | 5 | 4 | 3 | 2 | 1 |
| • Discuss the ocular and systemic safety aspects of anti-VEGF agents | 5 | 4 | 3 | 2 | 1 |
| • Use appropriate dosing regimens and imaging-guided treatment for nAMD in practice | 5 | 4 | 3 | 2 | 1 |

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know. _____

_____

2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice?
**4=definitely will implement changes 3=likely will implement changes 2=likely will not implement any changes 1=definitely will not make any changes**
4 3 2 1

Please describe the change(s) you plan to make: _____

_____

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face?

_____

_____

4. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity. ❑ Patient Care ❑ Practice-Based Learning and Improvement ❑ Professionalism ❑ Medical Knowledge ❑ Interpersonal and Communication Skills ❑ Systems-Based Practice

5. What other topics would you like to see covered in future CME programs? _____

_____

**ADDITIONAL COMMENTS** _____

_____

_____

**POST TEST ANSWER BOX**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
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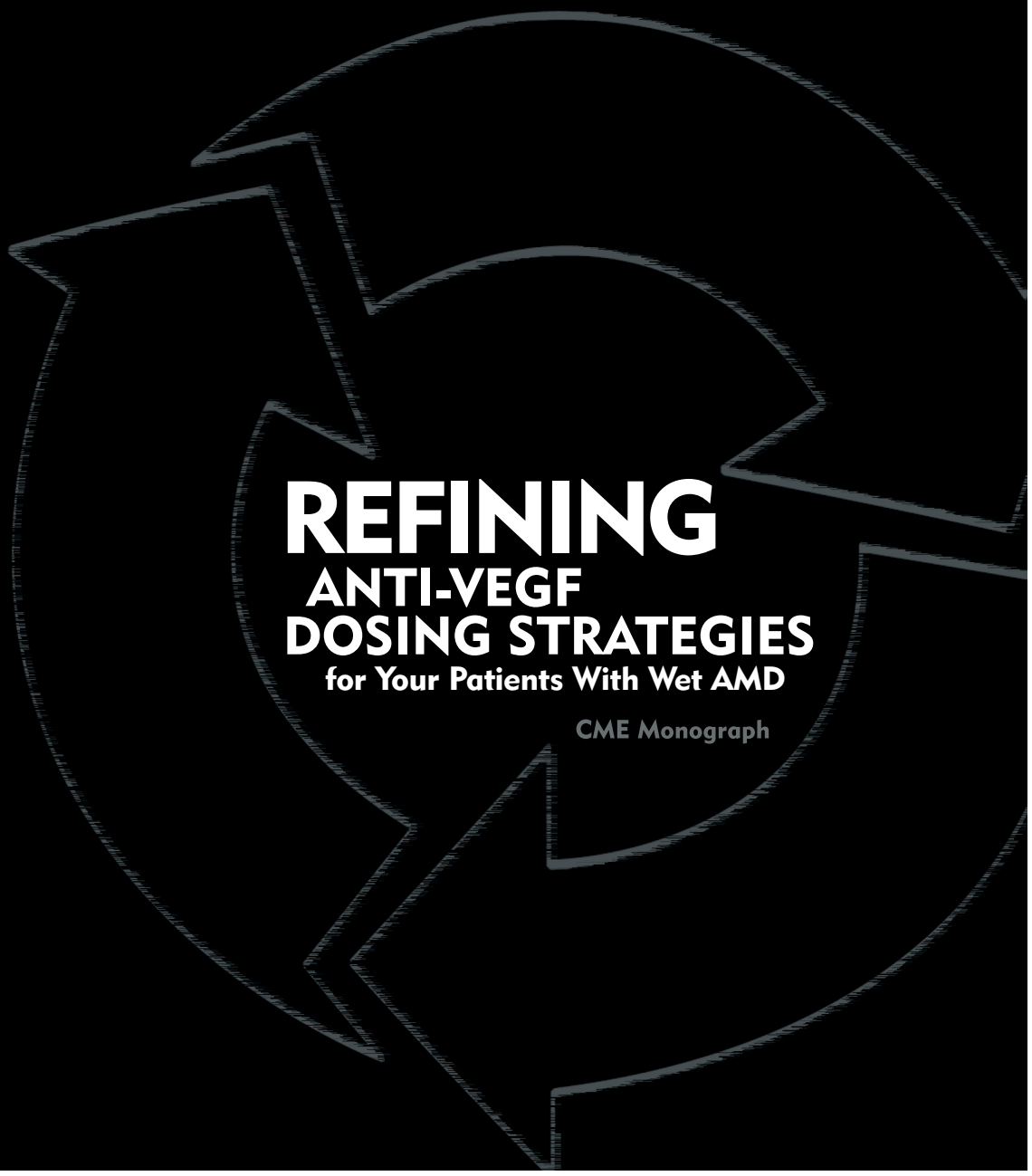

# REFINING ANTI-VEGF DOSING STRATEGIES

## for Your Patients With Wet AMD

CME Monograph