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Neovascular Age-Related Macular Degeneration

In this Issue...

The management of neovascular lesions associated with age-related macular degeneration (AMD) underwent a major paradigm shift when 2 pivotal phase 3 studies (MARINA, ANCHOR) showed that intravitreal administration of ranibizumab markedly reduced the likelihood of further vision loss and offered a reasonable opportunity for moderate vision improvement. Although ophthalmologists quickly adopted this intervention for the majority of their patients with subfoveal neovascular AMD lesions, they frequently departed from the monthly follow-up and treatment schedule through 24 months after treatment initiation in those trials. Most practitioners prefer to adapt delivery of this intervention to the clinical course of their individual patients through regular and frequent ocular coherence tomography scans.

In the last 6 months, several additional trials have been published comparing reduced-frequency, fixed-dosing regimens and variable dosing regimens with fixed monthly monitoring. These studies provide additional information intended to help ophthalmologists determine the risks and benefits of departing from mandatory monthly dosing for both vision and anatomic outcomes in their patients with neovascular AMD.

In this issue, we review the design, number of intravitreal injections and office visits, and efficacy outcomes in the EXCITE, SUSTAIN, and CATT studies to emphasize which follow-up and treatment regimens are successful and how they compare with one another.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Discuss the efficacy of mandatory monthly dosing of ranibizumab in patients with subfoveal predominantly choroidal neovascularization lesions, based on pivotal phase 3 studies of ranibizumab (MARINA, ANCHOR) vs. as needed regimens or reduced fixed frequency regimens
- Identify the various follow-up and treatment regimens used in other prospective clinical studies of ranibizumab (EXCITE, SUSTAIN) and the functional and anatomic outcomes of each
- Describe the design and outcomes of the CATT study, a noninferiority trial comparing fixed dosing every 4 weeks vs. variable dosing of both ranibizumab and bevacizumab in eyes with neovascular age-related macular degeneration lesions

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- **Neil M. Bressler, MD** has disclosed he has received grants/research support from Abbott Medical Optics, Inc., Allergan, Bausch & Lomb, BMS, Carl Zeiss Meditec, EMMES Corporation, ForSight Labs, LLC., Genentech, Genzyme Corporation, Lumenis, Notal Vision, Novartis, Ora, Inc., QLT,Inc., Regeneron, and Steba Biotech.

- **Susan Bressler, MD** has disclosed that she has received grants/research support from Bausch & Lomb, Genentech, Notal Vision, Regeneron and Novartis. She also has served as a consultant for GlaxoSmithKline.

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THIS ISSUE

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Susan B. Bressler, MD has disclosed that she has received grants/research support from Notal Vision, Genentech, Novartis, Bausch & Lomb, and Regeneron. Dr. Bressler has also served as a consultant for GSK.

Unlabeled/Unapproved Uses

The author has indicated that there will be references to unlabeled/unapproved use of intravitreal bevacizumab

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COMMENTARY

Phase 3 studies[1,2] have firmly established the efficacy of ranibizumab for treating choroidal neovascularization (CNV) from age-related macular degeneration (AMD) for lesions involving the center of the macula in which most of the lesion on fluorescein angiography is CNV rather than scar or hemorrhage. The efficacy of bevacizumab for treating similar lesions had been suggested by case series and small trials; however, the CATT study has provided a greater body of evidence to corroborate this conclusion. In fact, at 1 year, vision outcomes with every-4-week bevacizumab in CATT met the noninferiority definition to every-4-week ranibizumab proposed by the study design.

Despite the wealth of data that supports monthly dosing of antivascular endothelial growth factor (anti-VEGF) for neovascular AMD lesions, the treatment burden on patients, their caregivers, ophthalmologists, and health care systems has led to the continued need to identify alternative treatment options that would provide efficacy without compromising safety and the magnitude of the benefit that could be recognized with monthly intravitreal anti-VEGF injections.

Cumulative clinical evidence before CATT had shown that a monthly regimen of ranibizumab was associated with better treatment outcomes than less frequent dosing. This was confirmed in the EXCITE study, when fixed monthly dosing was directly compared with a loading phase of 3 consecutive monthly doses, followed by quarterly administration. This reduced-frequency dosing regimen did not meet the noninferiority criteria as outlined in the study design.

Eyes treated with monthly intravitreal injections also appeared to have greater improvement, on average, in visual acuity at 1 year and more stable reduction in central retinal thickness (CRT) on ocular coherence tomography (OCT) scans than did eyes in the less frequently dosed groups. In the SUSTAIN study, eyes treated on an as-needed individualized basis appeared to lose some of the early treatment benefits they attained with the mandated 3 consecutive doses of ranibizumab when they subsequently received variable dosing between months 3 and 12. The treatment burden was reduced for number

of injections, but not for monthly visits with regular use of diagnostic imaging. The criteria used to administer ranibizumab during the maintenance phase of the SUSTAIN study may have been too conservative (essentially, treat when worsening was documented, rather than continue treatment until no longer improving and then resume treatment if worsening occurs after this cessation), and tightening the criteria to include lesser degrees of disease activity, either functional or anatomical, might have led to better results.

Even in the CATT study, however, in which the dosing criteria in the variable treatment groups were much more liberal, and the number of doses administered in the first year of treatment may have been slightly higher (around 7 in CATT and 6 in SUSTAIN), the greatest improvement in visual acuity at 12 months appeared to favor the monthly ranibizumab treatment group, although it is unknown if these advantages are clinically relevant. Each of the point estimates of the difference in vision change at 12 months from baseline favored monthly ranibizumab over monthly bevacizumab injections or the use of either agent as needed. In addition, each of the OCT variables that were assessed favored monthly ranibizumab injections. This finding may have no clinical relevance, or it might translate into a greater difference in vision outcomes when patients complete their second year of follow-up if such findings are associated with a greater likelihood of declining visual acuity from year 1 to year 2. Fluorescein angiographic outcomes also demonstrated that a greater proportion of eyes treated with monthly vs. variable ranibizumab dosing stopped leaking and had no evidence of lesion growth at month 12. Again, this finding may have no clinical relevance, or it might translate into a greater difference in vision outcomes when patients complete their second year of follow-up if such findings are associated with a greater likelihood of declining visual acuity from year 1 to year 2.

Although investigations continue to help to determine the optimal treatment regimen of anti-VEGF agents for managing eyes with neovascular, especially if cost is an issue (either for the patient, from the perspective of the physician-patient relationship; or for society, from the perspective of public health and costs), the cumulative evidence to date suggests that adhering to monthly mandatory ranibizumab dosing may offer the individual patient the potential for the largest, most consistent, most stable vision gains, with supporting anatomic evidence of "drier" OCTs and angiograms with smaller lesions that are less apt to leak. Whether any increased benefits are clinically relevant to other regimens awaits additional results from two-year data from CATT and other studies. Monthly anti-VEGF therapy in neovascular AMD regimen obviates the need to perform regular imaging with any modality (such as OCT) and may shorten the length of office visits visits while slightly increasing the relatively low chance of endophthalmitis and potentially greatly increasing the drug costs. The annual burden of 12 to 13 office visits and 12 to 13 intravitreal injections, and the high cost of the agents, however, are real issues that drive our community (independent of the individual patient) to seek new and better ways to deliver effective anti-VEGF therapy to these patients.

Commentary References

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(14):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(14):1419-1431.

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RANIBIZUMAB FOR MINIMALLY CLASSIC OR OCCULT WITHOUT CLASSIC CNV LESION IN EYES WITH AMD: THE MARINA TRIALS

Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1419-1431.

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The multicenter, 2-year, double-blind, sham-controlled MARINA study evaluated ranibizumab—a recombinant, humanized, monoclonal antibody fragment (Fab) that blocks all active forms of VEGF-A—in eyes with either minimally classic or occult (ie, with no classic lesions) CNV from AMD. Patients received 24 monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) or sham injections. The visual acuity of all participants had to be 20/40 to 20/320 (Snellen equivalent) at study entry.

Follow-up of the 716 enrolled participants through 2 years resulted in nearly 95% of those receiving ranibizumab 0.5 mg avoiding moderate vision loss (defined as losing <15 letters from baseline visual acuity), compared with 62% of sham-injected individuals (P<.001). Moderate improvement in visual acuity (≥15 letters) was reported in 34% of participants in the ranibizumab 0.5-mg group and in only 5% of those in the sham group. The mean change in visual acuity increased rapidly during the first few months of treatment and stabilized at 7.2 letters gained in the ranibizumab 0.5-mg group at 12 months, with the magnitude of the treatment benefit sustained in the second year of treatment (6.6-letter increase) relative to baseline. In contrast, subjects in the sham-injection group experienced a decrease in visual acuity of 10.4 letters at 12 months and 14.9 letters at 24 months, relative to baseline. The mean initial level of visual acuity was approximately 20/80 in each of the treatment groups, among which 42% of eyes in the ranibizumab 0.5-mg group had 20/40 vision or better at 24 months, compared with 6% of eyes in the sham-injection group. Several fluorescein angiographic parameters favored the ranibizumab arm as well. The treatment was well tolerated in terms of serious ocular and systemic adverse effects.

This study demonstrated a treatment for neovascular AMD that not only was highly effective at preventing additional vision loss but was also capable of providing a meaningful improvement in visual acuity for a period of 2 years following presentation of symptoms. Rates of endophthalmitis, the most serious ocular adverse event associated with ranibizumab therapy, were reported to be about 1%, despite patients having received approximately 24 monthly intravitreal injections. Rates of anti-VEGF–specific side effects, such as hypertension, proteinuria, and arterial thromboembolic events (as defined by the Antiplatelet Trialists' Collaboration), did not appear to differ among the treatment groups. The only apparent difference was a greater proportion of nonocular hemorrhages in the ranibizumab 0.5-mg group vs. the sham-injection group (8.8% vs. 5.5%, respectively). Overall, this study heralded a new era in managing patients with the most common presentation of neovascular AMD, dramatically and favorably changing the prognosis for these people.

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RANIBIZUMAB FOR PREDOMINANTLY CLASSIC CNV LESIONS IN AMD: THE ANCHOR STUDY

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(14):1432-1444.

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The multicenter, 2-year, double-blind, active-controlled phase 3 ANCHOR study compared the safety and efficacy of ranibizumab vs. photodynamic therapy with verteporfin—the standard of care—in eyes with predominantly classic CNV lesions from AMD. Patients received 24 monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) plus sham verteporfin therapy, or monthly sham injections plus active verteporfin therapy. Verteporfin therapy (active or sham) was performed at study entry and repeated every 3 months, depending on the investigators' evaluation of fluorescein angiography. For study inclusion, participants had to have a lesion whose total size was ≤5400 µm in greatest linear dimension in the study eye and visual acuity of 20/40 to 20/320 (Snellen equivalent).

Among the 423 patients enrolled, 91% completed the primary outcome examination at 12 months. Moderate vision loss (a loss of ≥15 letters from baseline visual acuity on an Early Treatment Diabetic Retinopathy Study [ETDRS] chart) was avoided in 96% of those in the ranibizumab 0.5-mg group, compared with 64% of those in the verteporfin group (P<.001). In addition, vision improved ≥15 letters in 40% of participants in the ranibizumab 0.5-mg group vs. 6% of those in the verteporfin group (P<.001). The average change in visual acuity increased rapidly during the first several months of ranibizumab therapy, attaining a maximum level at month 9, which was sustained through month 12, at 11.3 letters of improvement, relative to baseline, in the 0.5-mg-dose group. In contrast, eyes receiving verteporfin therapy continued to experience vision loss throughout the first year of treatment, which reached a maximum at month 12, with an average loss of 9.5 letters from study entry. Although the initial level of visual acuity was a mean of approximately 20/100 in each treatment group, 39% of participants in the ranibizumab 0.5-mg group attained visual acuity of 20/40 or better at month 12, whereas only 4% of verteporfin-treated eyes achieved this outcome. Using fluorescein angiography, eyes receiving verteporfin manifested growth of CNV lesions and increase in area of leakage from CNV, as well as surrounding staining of the retinal pigment epithelium at month 12; whereas ranibizumab-treated eyes demonstrated reductions in each of these parameters. The rate of endophthalmitis was similar to that in the MARINA study, at 1.4% in the ranibizumab 0.5-mg group.

In eyes with the most aggressive form of predominantly CNV AMD lesions—that is, predominantly classic CNV—ranibizumab was shown to prevent central vision loss and potentially improve visual acuity more often than photodynamic therapy with verteporfin. The occurrence of serious ocular adverse events, as well as anti-VEGF–specific events of special interest, such as hypertension and cerebrovascular events, was uncommon. Rates of myocardial infarction (2.1%) and serious nonocular hemorrhage (2.1%) remained low but appeared to be higher among patients in the ranibizumab 0.5-mg group than in those in the verteporfin group (0.7% and 0%, respectively). As in the MARINA study, the results of the ANCHOR study changed the landscape of the management of eyes with subfoveal CNV, culminating in a reduction in the number of patients who become visually impaired or legally blind from AMD.

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A FLEXIBLE DOSING REGIMEN OF RANIBIZUMAB IN PATIENTS WITH NEOVASCULAR AMD: THE SUSTAIN STUDY

Holz FG, Amoaku W, Donate J, et al; SUSTAIN Study Group. Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. *Ophthalmology.* 2011;118(4):663-671.

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In an effort to achieve optimal visual acuity while avoiding monthly injections, a customized or individualized pro re nata (PRN, as needed) dosing regimen of ranibizumab was evaluated in eyes with a variety of predominantly CNV lesion compositions. The multicenter,12-month, phase 3, single-arm, open-label SUSTAIN study was designed to explore the safety, tolerability, and efficacy of using an OCT and visual acuity–guided PRN dosing regimen. In the initial loading phase, all participants received 3 consecutive monthly injections of ranibizumab (months 0 to 2), which was then followed by a PRN phase, in which additional treatment was administered at months 3 through 11, based on the investigators' assessment of disease progression. The retreatment criteria for these visits involved a loss in visual acuity of >5 letters or an increase in central retinal thickness (CRT) of >100 µm from the best levels attained at any visit. Additionally, an option was available to defer treatment if the patient's vision measured ≥79 letters (Snellen equivalent 20/25) or his/her CRT was ≤225 µm. In this study, the majority of participants received ranibizumab 0.3 mg, rather than ranibizumab 0.5 mg, at each treatment visit; the proportion of 0.5-mg injections administered during the study was 12.1%.

SUSTAIN enrolled a total of 513 patients. Follow-up at month 12 was excellent, at 89%. After participants received the required 3 injections, the mean number of additional intravitreal injections administered from month 3 through month 11 was 2.7 (range, 0 to 9), with a mean duration of treatment-free interval after the initial loading phase of 3.7 months. As in the MARINA and ANCHOR studies, baseline visual acuity had to be between 20/40 and 20/320 (Snellen acuity), with the mean visual acuity in the study group starting at 20/80. The pattern of vision change from baseline showed the customary rise in visual acuity during the first 3 months, with a gain of 5.8 letters. Visual acuity decreased slightly from month 3 to month 6 and remained stable from month 6 to month 12, attaining a net gain of 3.6 letters relative to baseline at month 12. The mean change in CRT was a loss of 101 µm at month 3 relative to baseline, which remained fairly constant through month 12. Safety results were comparable to those in the pivotal clinical trials summarized earlier.

The results of this study showed that 92% of participants had avoided moderate vision loss at month 12; thus, the PRN dosing regimen is a viable treatment option for accomplishing this goal. Although the improvement reported with this regimen appears to be lower than that reported in the MARINA and ANCHOR studies, improvement of at least 3 lines of visual acuity was observed in 19% of the cohort. Whereas MARINA and ANCHOR demonstrated a slight increase in visual acuity between months 3 and 12 (1.3 letters in each trial), in SUSTAIN, a pattern of deterioration between months 3 and 12 was observed. In retrospect, the authors question whether more sensitive retreatment criteria, such as a 50-µm, rather than a 100-µm, deterioration in CRT would have yielded better outcomes. In the absence of data, however, we do not have that information.

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REDUCED-FREQUENCY, FIXED-DOSING REGIMEN OF RANIBIZUMAB IN PATIENTS WITH NEOVASCULAR AMD: THE EXCITE STUDY

Schmidt-Erfurth U, Eldem B, Guymer R, et al; EXCITE Study Group. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE Study. *Ophthalmology.* 2011;118(5):831- 839.

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The EXCITE study was designed to demonstrate the noninferiority of a reduced-frequency, fixed-dosing regimen of 3 consecutive monthly doses (loading phase) of ranibizumab, followed by quarterly administration (maintenance phase), to a monthly regimen within the context of a phase 3b, 12-month, multicenter, randomized, double-masked, active-controlled trial. Participants with all predominantly CNV lesion compositions and visual acuity between 20/40 and 20/320 (Snellen equivalent) were enrolled and were assigned randomly to receive either 6 (0.3 mg or 0.5 mg) or 12 (0.3 mg) scheduled doses of ranibizumab. A noninferiority margin of -6.8 letters was selected for the change in vision at month 12 relative to baseline.

Among the 353 enrolled subjects, 86% completed the study and underwent assessment of visual acuity at month 12. Mean baseline visual acuity was approximately 20/80 in all treatment arms. In the per-protocol (PP) and the intent-to-treat (ITT) cohorts, the reduced-frequency, fixed-dosing regimen did not meet noninferiority compared with the monthly dosing regimen. In the PP population, visual acuity increased from baseline to month 12 by 3.8 letters in the ranibizumab 0.5-mg reduced-frequency dosing group, compared with an 8.3-letter increase in the ranibizumab 0.3 mg fixed monthly dosing group. The mean difference was -4.5 letters, with a 97.5% confidence interval (CI) of -8.4, -0.2. Although all treatment arms demonstrated a comparable increase in vision between study entry and month 3 (following the loading phase of the treatment regimen), patients treated with a quarterly dosing regimen, thereafter, lost vision (2.8 letters in the 0.5 mg group) during the maintenance phase (month 3-12), whereas the monthly fixed-dosing group continued to

gain vision (0.8 letters). In addition, the monthly dosing regimen showed a stable reduction in CRT throughout the maintenance phase, whereas the quarterly dosing groups demonstrated increases in CRT between treatments.

The PIER study had previously evaluated the same reduced-frequency, fixed-dosing regimen of ranibizumab in a smaller cohort without the benefit of a control group. The EXCITE study extends the observations of the PIER study, concluding that a quarterly dosing maintenance regimen of ranibizumab cannot maintain the initial gains realized during the loading phase, whereas a monthly dosing regimen can.

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RANIBIZUMAB VS. BEVACIZUMAB AND MONTHLY VS. VARIABLE DOSING IN PATIENTS WITH NEOVASCULAR AMD

CATT Research Group, Martin DF, Maquire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2011;364(20):1897-1908.

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This multicenter, single-blind, noninferiority trial addressed 2 issues regarding the current management of patients with neovascular AMD: (1) a comparison of ranibizumab vs. bevacizumab and (2) a comparison of monthly fixed dosing vs. an as-needed regimen with monthly evaluations. The primary outcome of the CATT study was the mean change in visual acuity at 1 year with a noninferiority limit of 5 letters. A total of 1208 participants had an entry visual acuity between 20/25 and 20/320 and had either subfoveal neovascular lesions or blood or fluid beneath the fovea. In addition to these 2 departures from the eligibility criteria of the pivotal phase 3 studies of ranibizumab, participants were also permitted to have predominantly blood lesions. Participants were randomly assigned to 1 of 4 treatment groups: (1) monthly ranibizumab, (2) ranibizumab with variable dosing, (3) monthly bevacizumab, or (4) bevacizumab with variable dosing. All participants were seen monthly, but only those assigned to the variable dosing groups underwent monthly time-domain OCT. Annual fluorescein angiograms were required. Retreatment was to be administered in the variable-dosing arms if there were signs of active CNV, such as fluid on OCT, new or persistent hemorrhage, decreased visual acuity compared with the previous examination, fluorescein leakage, or increased lesion size on angiography.

Baseline visual acuity was 20/60 (Snellen equivalent) across all treatment groups. The average number of treatments in the fixed monthly groups approached 12, whereas the as-needed groups received about 7 injections. Administration of monthly bevacizumab was shown to be noninferior to monthly ranibizumab, with gains of 8.0 and 8.5 letters, respectively, from study entry. Ranibizumab administered on an as-needed basis was also noninferior to monthly ranibizumab (6.8 letters; mean difference, -1.7 letters; 99.2% CI, -4.7, 1.3). Bevacizumab administered on an as-needed basis did not meet the noninferiority criteria, however, as the mean improvement was 5.9 letters (mean difference, -2.6 letters; 99.2% CI, -5.9, 0.8 letters relative to the gold standard of monthly ranibizumab. The mean decrease in CRT was likely is greatest with monthly ranibizumab. Several fluorescein angiographic outcomes also appeared to favor monthly ranibizumab administration over the as-needed ranibizumab regimen. No safety issues were identified between monthly vs. variable ranibizumab dosing; however, more serious systemic adverse events were reported among bevacizumab-treated patients vs. ranibizumab-treated patients.

The CATT study has provided evidence that the widely adopted strategy to treat neovascular AMD on an as-needed basis can yield visual acuity results at 1 year that are noninferior to monthly ranibizumab dosing, provided one administers ranibizumab (as the agent delivered) on an as-needed basis, and patients receive monthly OCT scans, assessments of changes in visual acuity relative to the most recent visit, and evaluation of fundus appearance (for the presence of new or persistent blood). Fluorescein

angiograms, if obtained, should also be acted upon if evidence of disease activity is present. Substituting monthly bevacizumab for monthly ranibizumab also can achieve vision results that are noninferior to (at least almost as good as) monthly ranibizumab. Although this substitution can drastically reduce the direct costs associated with disease management, it does not decrease the treatment burden and may expose patients to more systemic adverse effects.

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