

Antiangiogenic Approaches to Age-Related Macular Degeneration Today

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Intravitreal ranibizumab reduces the risk of visual acuity loss and increases the chance of visual acuity gain compared with no treatment or photodynamic therapy for selected cases of subfoveal choroidal neovascularization (CNV) in age-related macular degeneration (AMD). Although intravitreal ranibizumab did not result in substantial improvement (15 or more letters on an ETDRs chart) in the majority of cases treated in the MARINA (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab in the treatment of Neovascular AMD) or ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in AMD) trials, few cases experienced substantial visual acuity loss. The most serious known risk of treatment, endophthalmitis, although rare, is always a possibility. Intravitreal bevacizumab might be considered when ranibizumab is not available because of regulatory or financial constraints, and it might be considered in place of ranibizumab even without financial constraints if noninferiority trials show that bevacizumab is almost as good as—or is better than—ranibizumab. Systemic risks of intravitreal ranibizumab or bevacizumab are unknown, although trials have ruled out moderate or large systemic risks for ranibizumab. This therapy should be considered when initiating therapy for lesions that are subfoveal, and predominantly CNV when the lesion composition on fluorescein angiography (FA) is predominantly classic, or when there is presumed recent disease progression and the lesion composition is minimally classic or occult with no classic. Optical coherence tomography, FA, or both also might be of value to assist with decisions regarding continuation of treatment after it has been initiated. However, to date, there is little consistent information to suggest that utilizing these imaging modalities to consider withholding treatment before 2 years has been shown confidently to result in outcomes as good as monthly treatment. Extrapolation of these recommendations should be done with caution when considering the treatment of subfoveal CNV that is not predominantly CNV, such as predominantly blood lesions or lesions that are predominantly scar, as well as lesions associated with very low levels of visual acuity or those owing to causes other than AMD. A subsequent review in this series discusses other therapies for CNV being considered in the future.

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When considering the role of antiangiogenic approaches to age-related macular degeneration (AMD) today, one considers treatments used to initiate therapy for the neovascular stage of AMD. Vascular endothelial growth factor (VEGF) is a potent permeability factor and growth factor involved in the development of choroidal neovascularization (CNV).^{1,2} Inhibitors of VEGF represent a relatively new treatment for CNV. The most successfully tested anti-VEGF drug to date is intravitreal ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA), which has been shown to increase the chance of improving visual acuity by ≥ 15 letters (approximately ≥ 3 lines) in 25% to 40% of treated cases compared with controls in randomized clinical trials.^{3,4} Except for intravitreal bevacizumab (Avastin; Genentech, Inc), no other treatment evaluated in clinical trials approaches these chances of visual acuity gain, including laser photocoagulation,^{5,6} photodynamic therapy (PDT),⁷ submacular surgery,⁸ radiation,⁹ or pegaptanib sodium (Mucagen; Eyetech Pharmaceuticals, Inc, New York, NY).¹⁰

Ranibizumab

Ranibizumab is a recombinant, humanized, monoclonal Fab antibody fragment that inhibits all active forms of VEGF-A. The dosage of 0.5 mg given as a 0.05-cc intravitreal injection was approved in June 2006 for use in the treatment of AMD.³ The pivotal clinical trials with ranibizumab had 2 active treatment arms: 0.3 mg ranibizumab and 0.5 mg ranibizumab given as a monthly intravitreal injection in 0.05 cc monthly for 2 years compared with a monthly sham injection. Only the data with the 0.5 mg ranibizumab arm are presented here, because this is the dose most commonly marketed around the world, although the data with 0.3 mg ranibizumab were consistent with the 0.5 mg results.

Efficacy of Ranibizumab versus Photodynamic Therapy with Verteporfin for Predominantly Classic Subfoveal Choroidal Neovascular Lesions

Trial participants in the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal

Neovascularization in AMD) study had to meet specific criteria that could affect the generalizability of these results to cases that do not meet these criteria (see below), including age, best-corrected visual acuity, and AMD lesions of a specific size and composition on fluorescein angiography (FA).⁴ The CNV lesions had to be predominantly classic CNV ($\geq 50\%$ of the total area of the lesion was classic CNV).⁴ Unlike eligibility requirements for the MARINA (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD) study (see following section), participants were not required to have presumed recent disease progression (usually defined as presence of blood, documented recent loss of visual acuity, or documented recent growth of the choroidal neovascular lesion). Participants were assigned randomly to receive either (1) intravitreal ranibizumab 0.3 mg or 0.5 mg and sham-verteporfin (Visudyne; Novartis AG, Basel, Switzerland) therapy (intravenous infusion of saline), or (2) sham ranibizumab injections and active verteporfin therapy (intravenous verteporfin with laser irradiation of the lesion).⁴ Participants received the ranibizumab or the sham injections once monthly for 24 months. The verteporfin therapy or the sham verteporfin therapy was administered in the first month (day 0). Subsequent verteporfin therapy or sham verteporfin therapy was determined by the investigator, based on the results of angiography at months 3, 6, 9, 12, 15, 18, and 21.⁴ The protocol for measuring visual acuity involved a standardized refraction procedure and visual acuity testing protocol using an Early Treatment of Diabetic Retinopathy Study chart placed initially at 2 m.⁴

Mean visual acuity letter score at baseline was 47.1 (approximate Snellen equivalent of 20/125⁺²) in the 0.5-mg ranibizumab group and 45.5 (20/125) in the placebo group. For the primary outcome (visual acuity decline of <15 letters from baseline at 12 months), 96.4% of the 0.5-mg group ($n = 140$) and 64.3% of the verteporfin group ($n = 143$) avoided this loss ($P < 0.001$).⁴ These outcomes were maintained at 24 months for most subjects, with 89.9% of the 0.5-mg group and 65.7% of the verteporfin group avoiding a loss of ≥ 3 lines.¹¹ Investigators also reported that visual acuity improved by ≥ 15 letters in 40.3% of the 0.5-mg group, as compared with 5.6% of the verteporfin group ($P < 0.001$) at 12 months⁴ and 41.0% of the 0.5-mg group gained ≥ 3 lines of visual acuity versus only 6.3% of the verteporfin group at 24 months.¹¹ Differences in the mean visual acuity from baseline visual acuity were noted as early as 1 month, when 8.4 letters of improvement occurred in the 0.5-mg ranibizumab group compared with 0.5 letters in the PDT group ($P < 0.001$).⁴ At 12 months, mean visual acuity improved by 11.3 letters in the 0.5-mg ranibizumab group but decreased by a mean of 9.5 letters in the verteporfin group ($P < 0.001$).⁴ At 24 months, mean visual acuity improved by 10.7 letters in the 0.5-mg ranibizumab group, but decreased by 9.8 letters in the verteporfin group.¹¹

Although PDT produced outcomes that likely were better than the natural course of the disease,⁷ the 24-month data reinforced the conclusions of the 12-month data previously published and indicated that the increased chance of avoiding ≥ 15 -letter loss and of gaining ≥ 15 letters with monthly

intravitreal ranibizumab persisted through at least 2 years compared with standard applications of PDT.

Efficacy of Ranibizumab versus Sham Treatment for Minimally Classic or Occult with No Classic Subfoveal Choroidal Neovascular Lesions and Presumed Recent Disease Progression

In a Phase 3, double-blind, sham-controlled, randomized clinical trial, eligibility criteria included subfoveal CNV with lesion composition on FA that was minimally classic or occult with no classic component accompanied by presumed recent disease progression.³ Participants were assigned randomly to either sham injections or intravitreal injections of ranibizumab (either 0.3 or 0.5 mg) for 24 months.³ Visual acuity was measured using an Early Treatment of Diabetic Retinopathy Study chart and a standardized refraction and testing protocol, with initial chart placement at 2 m.³

Mean visual acuity letter score at baseline was 53.7 (20/80⁻¹) in the 0.5-mg ranibizumab group and 53.6 (20/80⁻¹) in the sham injection group.³ Using the primary outcome of visual acuity decline of <15 letters from baseline as a measure of efficacy, 94.6% of those in the 0.5-mg ranibizumab group and 62.2% of those in the sham injection group met the primary goal ($P < 0.001$) after 12 months of treatment.³ At 24 months, 90.0% of those in the 0.5-mg ranibizumab group and 52.9% of those in the sham injection group met the primary goal ($P < 0.001$).³

At 12 months, visual acuity improved by ≥ 15 letters in 33.8% of the 0.5-mg ranibizumab group, as compared with 5% of the sham injection group ($P < 0.001$).³ Participants in the 0.5-mg ranibizumab group achieved mean increases in visual acuity of 7.2 letters, whereas the sham injection group lost an average of 10.4 letters ($P < 0.001$).³ At 24 months, participants in the 0.5-mg ranibizumab group gained a mean of 6.6 letters of visual acuity, compared with a mean loss of 14.9 letters in the sham injection group ($P < 0.001$).³

In addition to experiencing improvements in objectively measurable visual outcomes, at 12 months patients treated with ranibizumab were more likely to improve with respect to self-reported vision-related quality of life. This information is complementary to the visual acuity outcomes described; although most physicians and patients make decisions based on functional parameters such as a patient's ability to read, watch television, and avoid dependence on others because of vision, the primary outcome measure in most recent trials evaluating treatments for neovascular AMD has been visual acuity in the treated eye.^{3-6,8,10} Although changes in visual acuity on an eye chart are important in understanding treatment effects, measures of visual acuity do not always completely capture the degree of visual function. Clinicians may assume that visual function or patient's perception of visual function improves along with visual acuity; however, this is not always the case.¹² Among MARINA participants, scores on the National Eye Institute Visual Function Questionnaire 25 relating to activities that require both near vision (such as sewing) and distance vision (such as watching television) were more likely to

improve by ≥ 10 points, a clinically relevant amount, in the ranibizumab group than in the sham injection group ($P < 0.001$).¹³ In addition, ranibizumab-treated patients were less likely to perceive themselves as being dependent on others because of their vision.¹⁴ Similar results were confirmed in the ANCHOR trial.¹⁵

Safety

Safety issues with ranibizumab intravitreal injections include local ocular adverse events (AEs) from the drug or the injection, as well as potential systemic AEs of the drug.¹⁶ Ocular AEs may be categorized as common but not serious and rare but potentially serious. The AEs that are considered common but not serious include subconjunctival hemorrhage, vitreous floaters from medication or vitreous hemorrhage, and discomfort from antiseptic used to prepare the cornea before the injection.¹⁶ Endophthalmitis is a rare but potentially serious ocular AE that may develop after any intravitreal injection, regardless of what is being injected. Just how much preparation is necessary to minimize the development of postinjection infections is controversial. It is unknown if pretreatment antibiotics are necessary for several days before the procedure or on the day of the procedure to reduce the risk of endophthalmitis. Furthermore, it is unknown if posttreatment antibiotics are necessary to maintain sterile conditions for the injection. All agree that the use of a lid speculum and povidone-iodine treatment of lids, lashes, and the area to receive the injection are generally recommended.¹⁷ Other rare but serious ocular AEs include inflammation (as opposed to infection), vitreous hemorrhage, retinal tear or detachment, and increased intraocular pressure, which in the trials was listed as a serious AE, but might not always be considered a serious AE by a treating ophthalmologist.¹⁶

Systemic AEs are a concern; VEGF inhibitors that cross into the general circulation can compromise functions that rely on VEGF outside of the eye, such as wound healing and the formation of new blood vessels around the heart or brain in cases of ischemia.^{18,19} Patients with AMD already are at higher risk of cardiovascular disease than the general population by virtue of their age and the association of AMD with systemic hypertension,^{20,21} and patients with such risk did not have to be excluded from participating in ANCHOR or MARINA.^{3,4} Consequently, participants in clinical trials of VEGF inhibitors were carefully monitored for possible increases in blood pressure, occurrence of myocardial infarction/stroke, and nonocular hemorrhages.^{3,4}

There was no evidence that ranibizumab 0.5 mg was associated with increases in either diastolic or systolic blood pressure. In fact, treatment-related hypertension emerged in a larger proportion of PDT patients (12/143 [8.4%]) than among ranibizumab 0.5-mg patients (9/140 [6.4%]).⁴ Among participants in the MARINA trial, approximately

16% in both the ranibizumab 0.5 mg and sham injection groups developed hypertension.³

Nonocular hemorrhages include events such as cerebral or gastrointestinal bleeding. In the ANCHOR trial, nonocular hemorrhage was more frequent in the 0.5-mg ranibizumab group (6.4%) than in the PDT group (2.1%).⁴ In the MARINA trial, the cumulative frequency of nonocular hemorrhage by month 24 was 5.5% (13/236) in the sham injection group compared with 8.8% (21/239) in the 0.5-mg ranibizumab group.³

Ranibizumab is a recombinant monoclonal antibody that contains both mouse- and human-derived segments.²² The human segments are engineered into the monoclonal antibody to minimize the chance that the patient's immune system will react against the monoclonal antibody.²² Nevertheless, some patients treated with ranibizumab may develop antibodies to it. Thus, ranibizumab trials include routine testing of participants for antibodies to ranibizumab using an electrochemiluminescent assay.

In the ANCHOR trial, 8% of ranibizumab 0.5-mg subjects and 1.5% of subjects with PDT had low levels of antibodies to ranibizumab at baseline.⁴ At trial conclusion, 3.9% of ranibizumab 0.5-mg subjects had developed antibodies to ranibizumab compared with 0% in the PDT group. In the MARINA trial, none of the subjects in the 0.5-mg ranibizumab group and 0.5% of those in the sham injection group had antibodies to ranibizumab at baseline.³ After 24 months, 6.3% of subjects treated with ranibizumab 0.5 mg and 1.1% of those in the sham injection group developed antibodies to ranibizumab.³

The clinical implications of baseline and postexposure immunoreactivity to ranibizumab are unclear. Although the numbers were small, subjects in the ANCHOR trial who were immunoreactive were more likely to develop inflammation than those who were not.⁴

With respect to cardiovascular or cerebrovascular events, during the ANCHOR trial, 1 subject in the PDT group (0.7%) and 3 subjects in the ranibizumab 0.5-mg group (2.1%) developed nonfatal myocardial infarctions, although the events occurred at times that were unrelated to treatment.⁴ The frequency of stroke (1 in each group) and cerebral infarction (0 in each group) in the ANCHOR trial were too low to draw meaningful conclusions.⁴

At 24 months, the overall frequency of cardiovascular systemic events in the MARINA trial was similar in the 0.5-mg ranibizumab and sham injection groups.³ There were only small differences in the frequency of thromboembolic events between the sham injection group (3.8%) and the ranibizumab 0.5-mg group (4.6%).³ The frequency of death (2.5%) was the same in the ranibizumab 0.5-mg and sham injection groups.³ Two individuals in each group died of stroke.³

An interim safety analysis of data from the SAILOR (Safety Assessment of Intravitreal Lucentis for AMD) trial²³ indicates that the frequency of stroke among subjects randomly assigned to receive 0.5 mg of ranibizumab is 1.2%, compared with 0.3% among those assigned to treatment with 0.3 mg ranibizumab. Subjects with a previous history of stroke may have been at higher risk of a second stroke. There was no significant difference in the frequency of

myocardial infarction between the 2 treatment groups in the SAILOR trial.

Although event rates for these cerebrovascular or cardiovascular events seem to be low with ranibizumab, ophthalmologists should ensure that patients understand the theoretic potential for these risks. Additional studies over time may help to refine understanding of the magnitude, if any, of this risk.

Is There a Role for Bevacizumab in Place of Ranibizumab?

Bevacizumab is approved by the US Food and Drug Administration for intravenous use in the treatment of cancers such as colorectal cancer and non-small-cell lung cancer. Using bevacizumab as an intravitreal injection to treat neovascular AMD is off-label at this time. Many ophthalmologists, however, appropriately offer intravitreal bevacizumab to AMD patients based on multiple forms of evidence: results from several retrospective case series of up to 79 cases,^{24–27} extrapolation from the magnitude of the outcomes reported with ranibizumab versus sham treatments or PDT, the structural similarity between ranibizumab and bevacizumab, the anecdotal experience of ophthalmologists who observe rapid resolution of abnormalities on optical coherence tomography (OCT) and fluorescein leakage from CNV within a month of treatment that are not seen with most other treatments, and the natural history of the disease if left untreated. Although this evidence is not as strong as a randomized, clinical trial (currently enrolling subjects in the CATT, sponsored by the National Eye Institute) to provide confidence regarding the precise risks and benefits of bevacizumab, or whether bevacizumab is almost as good, better, or actually worse than ranibizumab, the improvement seen in some cases among just 10 or 20 patients in a practice seems far greater than one would see with the natural course, PDT with verteporfin, or intravitreal pegaptanib.

There also are theories that the larger size of bevacizumab relative to ranibizumab may result in bevacizumab not clearing as quickly from the eye, potentially resulting in longer duration of activity. To the knowledge of this author, this claim has not been confirmed. Also, studies evaluating the use of bevacizumab for diabetic macular edema in randomized clinical trials²⁸ did not suggest that the effects of the drug, on average, last longer than the 4 weeks proposed for ranibizumab. Also, any potential safety concerns of a larger size biologic remain unknown. Ophthalmologists are assuming, based on case series evidence and in the absence of a noninferiority trial, that bevacizumab is at least almost as good as ranibizumab with respect to efficacy and safety. The choice of bevacizumab may be driven by situations in which ranibizumab is not available (e.g., before approval by a regulatory agency) or not affordable for a patient. Some ophthalmologists also might recommend bevacizumab in place of ranibizumab, even when it is available and affordable to the patient, because of concerns regarding the administrative costs to a practice associated with the large revenues and expenditures of

ranibizumab, or the cost to society (e.g., taxpayers' payments for Medicare), although to the knowledge of this author, there is no strong evidence to support this supposition at this time.

Looking at the available data—for example, in 1 retrospective case series—79 subjects received 1.25 mg of intravitreal bevacizumab monthly for 4 to 15 weeks.²⁶ Mean central subfield retinal thickness measured by OCT in the 51 subjects available for follow-up at week 8 declined by 89 μ m from baseline.²⁶ Subjects experienced improvement in mean visual acuity ($n = 51$) from 20/200 to 20/125 at week 8.²⁶

In another prospective case series, Bashshur et al²⁷ injected 2.5 mg of bevacizumab (twice the dose given by others^{24–26}) into the vitreous in 17 AMD patients with CNV at baseline, week 4, and week 8.²⁷ Visual acuity was measured with a Snellen chart; mean best-corrected visual acuity was 20/252 at baseline and 20/76 at week 12 ($n = 17$).²⁷ Mean central subfield retinal thickness also improved between baseline and week 12 in all 17 patients.²⁷

Safety of Bevacizumab

Data on the safety of intravitreal bevacizumab are more limited than data on ranibizumab safety because there have been no large, prospective safety studies of this medication with follow-up of at least 1 to 2 years. Among a retrospective case series of 266 patients, 2 (0.8%) developed mild vitritis after 1 month of exposure to bevacizumab. Both episodes resolved spontaneously. At month 3, there was no evidence of endophthalmitis, retinal tears, or increased intraocular pressure. No ocular side effects were noted in 17 patients treated with bevacizumab at twice the dosage used by Avery et al²⁶ (2.5 vs 1.25 mg). There was also no significant increase in intraocular pressure or progression of cataract. In a retrospective case series, 79 patients received intravitreal bevacizumab monthly for 4 to 15 weeks. The authors report that bevacizumab does not contain preservatives, some of which are known to be toxic to the eye. Patients in this series did not develop uveitis, endophthalmitis, or ocular toxicity. In a subsequent case series (Wu et al²⁹), no additional safety concerns were reported among 1265 consecutive patients retrospectively reviewed.

With respect to systemic safety of bevacizumab, in the retrospective series of 79 AMD cases, there were no thromboembolic events or hypertension. This small study, however, was not powered to identify AEs unless they occurred in >4% of trial participants. In a 3-month retrospective study of bevacizumab treatment in 266 patients, 1 (0.4%) developed a nonfatal myocardial infarction after the third injection. Two patients (0.8%) had apparent transient ischemic attacks (diagnosis was not definitive); however, both recovered with no sequelae. There were 2 deaths, one from myocardial infarction. Although that patient was a smoker with a history of emphysema, the authors stated that death may have been treatment related. It is important to consider, however, that this population (mean age, 80.3 years) is at risk for myocardial infarction regardless of treatment, and that a case series of 266 patients may not

be powered adequately to identify rare events. There were no thromboembolic events noted during the 12-week study by Bashshur et al.²⁷ With only 17 patients, this study had little power to identify anything other than very common AEs.

Role of Fluorescein Angiography When Considering Initiation of Therapy for Choroidal Neovascularization

Because ranibizumab has been shown to be beneficial whether the lesion composition was predominantly classic, minimally classic, or occult with no classic features, and because treatment benefits (although not necessarily benefits that are almost as good) with bevacizumab likely apply to these different lesion compositions, one might ask whether FA is needed in the management of CNV in AMD. Several circumstances warrant obtaining an FA when diagnosing CNV from an ocular history and examination. First, if it is not certain that the lesion extends under the center of the macula, FA can determine if the lesion is well demarcated and does not extend under the center of the macula, in which case laser photocoagulation might be considered.³⁰ If it is certain that the lesion extends under the center of the macula, FA is still indicated for several reasons. One reason is to confirm that the diagnosis is indeed CNV. Although the presence of subretinal fluid, hemorrhage, blood, and elevation of the retinal pigment epithelium in the presence of drusen may be indicative of CNV, several masquerades for CNV could be present that, if diagnosed, could avoid monthly injections of ranibizumab or lead to other treatments. These masquerades could include subretinal fluid from central serous chorioretinopathy, lipid or retinal thickening from diabetic macular edema, progressive fluorescein staining of vitelliformlike material in retinal pigment epithelial abnormalities consistent with a pattern dystrophy of the retinal pigment epithelium, or subretinal hemorrhage from a macroaneurysm.

Another reason to consider FA is to determine the lesion composition. Subjects with predominantly classic lesions were enrolled in the Treatment of Age-related Macular Degeneration with Photodynamic Therapy Investigation,⁷ regardless of whether there was recent disease progression, and with this approach, approximately 95% of the cases treated with ranibizumab avoided loss of ≥ 15 letters. For minimally classic or occult with no classic features lesions, only lesions with presumed recent disease progression were enrolled. The MARINA results seem to provide a strong rationale for requiring recent disease progression; despite requiring this presentation, only 35% of the sham-treated cases lost ≥ 15 letters of visual acuity. If cases were added without recent disease progression, the sham group may have been closer to the 95% rate of avoiding the ≥ 15 letter loss noted with ranibizumab. Also, potentially fewer cases than 25% to 34% may have improved by ≥ 15 letters in the ranibizumab group if cases without recent disease progression were enrolled. Thus, an angiogram may be useful in determining whether treatment should be commenced promptly regardless of whether there was recent disease

progression (for predominantly classic lesions) or if the decision to treat should be influenced by the absence of recent disease progression (for minimally classic or occult with no classic features lesions).

Even if it is relatively certain that the lesion extends under the center of the macula, is indeed CNV, and has recent disease progression because of visible blood or recent visual acuity loss, FA may be desirable if therapy may be withheld in the future when a case seems no longer to be improving or cannot improve further. To know if a neovascular lesion is not growing or no longer improving or cannot improve further, one needs an FA when considering withholding additional treatment, and needs to compare it with an angiogram from the last time that the lesion was treated.

Treatment Algorithm for Initiating Therapy with Ranibizumab (or Bevacizumab) for Subfoveal Choroidal Neovascularization in Age-Related Macular Degeneration

Figure 1 shows that the approach to the management of CNV can begin with FA to determine the extent of the lesion based on standardized published interpretations.^{31–33} Determining the extent of the lesion facilitates determining its location, with respect to the center of the macula, as well as its composition.

If the lesion is well demarcated and not under the center of the macula, laser photocoagulation to the entire lesion can be considered, as was done in the Macular Photocoagulation Study.³⁰ If the lesion extends under the center of the macula, or if the scotoma from laser photocoagulation might be noticeable because of the proximity of the posterior extent of the lesion with respect to the center of the macula, then lesion composition must be determined. If the lesion is predominantly classic, then one might initiate therapy with ranibizumab or bevacizumab. If the lesion is predominantly CNV but with a lesion composition that was minimally classic or occult with no classic CNV, then careful monitoring for progression or change to a predominantly classic lesion might be appropriate, rather than initiating ranibizumab or bevacizumab. However, the interval between evaluations should be close enough (perhaps starting with 3 weeks) to make it unlikely that substantial progression might occur before therapy was initiated for progression or change to a predominantly classic lesion. If the lesion composition is minimally classic or occult with no classic features and there is presumed recent disease progression, then initiating therapy with ranibizumab or bevacizumab is supported by the evidence in the literature.

Choroidal Neovascular Lesions Not Evaluated in Large Randomized Trials Testing Ranibizumab or Bevacizumab

When determining whether to extrapolate results of MARINA and ANCHOR to CNV lesions not included in those trials, evidence-based medicine guides suggest extrapolating

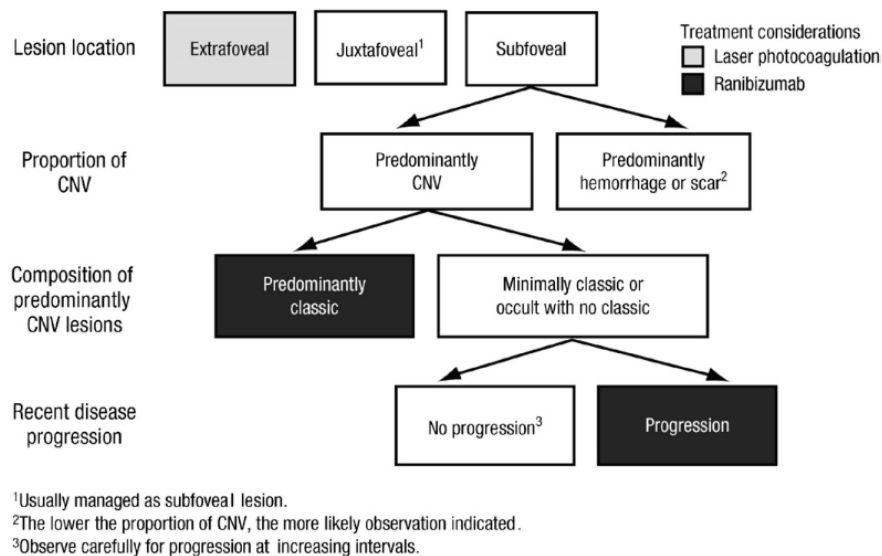


Figure 1. Management of choroidal neovascularization in age-related macular degeneration. CNV = choroidal neovascularization.

unless there is a reason to suspect that the results from the trials guiding treatment (in this case, MARINA and ANCHOR) may not apply to the case being considered. There are numerous circumstances of choroidal neovascular lesions for which ranibizumab or bevacizumab might not be considered, or in which other therapies might be considered as well.

Lesions that are predominantly blood or scar (Fig 1) were not included in the MARINA or ANCHOR trials. For predominantly blood lesions, one may not want to extrapolate results of MARINA or ANCHOR trials, because these lesions may be the result of a tear of the retinal pigment epithelium, where the prognosis may be different from cases that did not present with large tears of the retinal pigment epithelium in MARINA or ANCHOR.³⁴ Also, the blood can sometimes have a toxic effect on the overlying retina.³⁵ For lesions that are predominantly scar, which also were excluded from MARINA and ANCHOR, the results of MARINA or ANCHOR may not apply. Predominantly scarred lesions may not deteriorate as often as lesions that were predominantly CNV in MARINA and ANCHOR. Such predominantly scarred lesions may have a visual acuity course that is closer to the natural course of lesions starting at year 2 or 3, when little additional visual acuity loss occurred,^{30,36} so that it would be unlikely to have a greater risk of deteriorating than it would with ranibizumab or bevacizumab. Furthermore, such lesions may have little chance of improvement; there is no evidence, to our knowledge, of substantial improvement of visual acuity in predominantly scarred lesions after ranibizumab or bevacizumab treatments.

Other lesions for which extrapolation may not be appropriate include lesions with very low levels of visual acuity (e.g., <20/400). For such lesions, variability in visual acuity measurements may require improvements or deteriorations

of a minimum of 20 or 25 letters to be confident of a real change,^{37,38} and this minimal amount of change may not be relevant at very low levels of visual acuity. Also, subfoveal CNV not owing to AMD (e.g., owing to pathologic myopia) may have a different natural course or may have a better response to other therapies such as PDT, again requiring caution before extrapolating the results of MARINA or ANCHOR to such lesions.

Other Antiangiogenic Approaches to Age-Related Macular Degeneration

In clinical trials evaluating pegaptanib 0.3 mg administered into the vitreous, approximately 70% of the subjects avoided loss of ≥ 15 letters, which is of similar magnitude to results seen with PDT.¹⁰ However, the use of pegaptanib seems to have been largely superseded by ranibizumab (or bevacizumab) based on the evidence described. The article in this monograph by Diana Do describes the potential role of other antiangiogenic drugs, either alone or in combination with ranibizumab. That article also contains updates on interventions for neovascular AMD that are not based on VEGF inhibitors.

Management of Neovascular Age-Related Macular Degeneration after Initiating Antivascular Endothelial Growth Factor Therapy

Results from large-scale, randomized clinical trials, such as MARINA and ANCHOR, which provide the strongest evidence to support the initiation of anti-VEGF therapy for

neovascular AMD, are based on monthly treatments for 2 years. One of the challenges to this therapy is to try to determine whether a regimen can be identified that may allow less frequent treatments and less frequent visits without compromising visual acuity outcomes. The PIER study (Regillo et al³⁹), which tested a reduced-frequency, fixed-dosing regimen of ranibizumab every 3 months after 3 monthly treatments had been given, was shown to be superior to sham treatment. However, the improvement in mean visual acuity through month 3 was not sustained to month 12. The proportion of subjects with substantial improvement (≥ 15 letters) was not superior to sham treatment. Thus, this reduced-frequency, fixed-dosing schedule was much more likely to avoid substantial vision loss than sham treatment, but not more likely to result in substantial vision improvement, in contrast with the frequency of substantial improvement seen in MARINA and ANCHOR. Although the different outcomes with PIER vs MARINA and ANCHOR could have been due to the different populations evaluated, a subsequent randomized trial comparing monthly 0.3 mg ranibizumab to a reduced-frequency, fixed-dosing schedule (Silva R. Safety and efficacy of 2 ranibizumab dosing regimens in neovascular age-related macular degeneration patients: 12-month results of the EXCITE study, presented at the Euretina Meeting 2009, May 16, Nice.) showed superior outcomes with respect to mean improvement in visual acuity from baseline for monthly compared with less frequent treatment.

Yet another study, utilizing OCT to guide retreatment decisions and presented at the Association for Research in Vision and Ophthalmology's Annual Meeting in May 2009 (Holz FG. Safety and efficacy of ranibizumab treatment in patients with neovascular age-related macular degeneration: 12-month results of the SUSTAIN study. Presented at: Association for Research in Vision and Ophthalmology 2009, May 5, Fort Lauderdale.), again showed a loss in the mean visual acuity gain from month 3 to month 12 in the group randomized to a regimen that considered OCT information to guide retreatment after month 3 compared with monthly treatments through month 12. Although this trial seemed to have better outcomes with respect to improvement in visual acuity compared with a reduced-frequency dosing regimen compared with the PIER regimen, the trial involved monthly evaluations to determine whether retreatment was to be performed. In other words, although fewer treatments were applied in the group assigned to retreatment based on OCT after month 3, treatment visits remained monthly.

Whereas another study using both monthly OCT and occasional FA suggested similar outcomes with respect to vision improvement,⁴⁰ the confidence intervals around the results with <45 subjects were wide so that one could not state confidently that the chance of substantial improvement was similar. Furthermore, there was no comparison group with monthly treatment to know how these subjects would have done with monthly treatment. In addition, these results have not been confirmed in a subsequent, similarly designed study.⁴¹ One additional study, HORIZON (Singer M. HORIZON extension trial of ranibizumab for neovascular age-related macular degeneration: two-year safety and

efficacy results. Presented at: Association for Research in Vision and Ophthalmology 2009, May 5, Fort Lauderdale.) evaluated whether investigators could sustain improved visual acuity results beyond 2 years of monthly treatment using clinical judgment and whatever imaging the investigator judged was appropriate to make retreatment decisions. Among 481 subjects 2 years after entry into MARINA, ANCHOR, or FOCUS (RHuFab V2 ocular treatment combining the use of visudyne to evaluate safety) trials, median visual acuity had improved by approximately 10 letters (from 20/80 to 20/50); in addition, the median visual acuity had been relatively stable from 1 to 2 years after initiating monthly treatment. However, 1 year after entry into HORIZON, when monthly treatments were replaced by retreatment decisions by the investigator, median visual acuity decreased by 5 letters to 20/63; 2 years after entry into HORIZON, median visual acuity decreased by another 3 letters.

In summary, although treatments that occur less than monthly seem to increase the chance of avoiding substantial visual acuity loss, the chance of substantial visual acuity gain seems less likely than with monthly treatment, regardless of whether a reduced-frequency, fixed-dosing schedule is used, or a retreatment decision based on OCT alone or OCT and other parameters such as FA. Even if a regimen can be determined that can sustain the chance of substantial visual acuity improvement attained with monthly treatments, frequent visits to assess whether treatment is given seem to be needed, and OCT alone, as performed in the studies described (usually consisting of time domain OCT), does not seem to be sufficient to identify the need for treatment that results in a sustained chance of visual acuity improvement.

Conclusion

In summary, intravitreal ranibizumab reduces the risk of visual acuity loss and increases the chance of visual acuity gain compared with no treatment or PDT for selected cases of subfoveal CNV in AMD. The benefits seem to outweigh the risks at this time. Bevacizumab might be considered when ranibizumab is not available owing to regulatory or financial constraints, and it might be considered in place of ranibizumab even without financial constraints if noninferiority trials show that bevacizumab is almost as good or better than ranibizumab. Ranibizumab or bevacizumab should be considered when initiating therapy for lesions that are subfoveal and predominantly CNV, when the lesion composition is predominantly classic, or when there is presumed recent disease progression and the lesion composition is minimally classic or occult with no classic features. An FA is needed to confirm the diagnosis and to determine whether laser photocoagulation might be indicated when the lesion is well demarcated, not extending under the center of the macula, and symptomatic. In addition, FA is needed to determine the lesion composition, which can affect decisions to initiate therapy (Fig 1), and might be of value to assist with decisions regarding continuation of treatment after it has been initiated. Extrapolation of these results should be done with caution when considering the treatment

of subfoveal CNV that is not predominantly CNV, such as predominantly blood lesions or lesions that are predominantly scar, as well as lesions associated with very low levels of visual acuity or attributable to causes other than AMD. The available evidence does not support the use of other antiangiogenic therapies approved by the US Food and Drug Administration (specifically pegaptanib at this time) over the use of ranibizumab or bevacizumab in most cases. As mentioned, other articles in this series discuss the basic concepts of outcome measures to assess efficacy of treatments of neovascular AMD, as well as other therapies for CNV being considered in the future.

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