

NAVIGATING AMD TREATMENT OPTIONS: PRACTICAL ANSWERS TO COMPLEX QUESTIONS*

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ABSTRACT

Although level 1 scientific evidence for vascular endothelial growth factor (VEGF) inhibitors in age-related macular degeneration has existed for several years, many patients are baffled by our recommendations for treatment when they report no improvement in visual outcomes with these treatments. Ranibizumab offers the chance for not only maintaining visual function but also, in some patients, improving visual acuity. In general, physicians can expect most patients to maintain or improve visual acuity, with an approximately 33% chance of 3-line improvement. However, for patients, quality of life is a more tangible benefit than visual acuity scores, and the ranibizumab studies show that quality-of-life measures can improve with this treatment, even if the worse-seeing eye is treated. This article discusses the results of quality-of-life measures with ranibizumab treatment and addresses some of the most common questions about anti-VEGF therapies posed by patients and referring physicians. A discussion of current studies of combination therapy is also included.

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An important challenge for ophthalmologists is the disparity between scientific evidence (ie, level 1) to support the new treatments for subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) and patient perception of efficacy. Although randomized, controlled trials of vascular endothelial growth factor (VEGF) inhibitors showed statistically significant differences in outcomes, patients receiving these treatments did not report vision improvements. This presented a challenge for ophthalmologists treating AMD, especially as they tried to argue in favor of treatment to delay or avoid further visual loss. Moreover, the definition of “visual acuity” or visual function can be different for patients as they struggle to maintain an acceptable quality of life, compared to clinical researchers, who measure this endpoint based on lines or letters on the eye chart. The newer treatments for AMD, notably ranibizumab, now offer the chance for not only maintaining visual function but also, in some patients, improved visual acuity. For ophthalmologists, this evolution in patient perception and clinical experience is refreshing, but treating physicians need to be prepared to offer realistic answers to patient and referring-physician questions on expected outcomes and quality-of-life issues.

PATIENTS’ EXPECTATIONS OF TREATMENT EFFECT

Patients evaluate a treatment for AMD based on how it will impact their daily lives, not on a number of lines or letters in an eye examination. This is an important distinction when considering efficacy of a particular treatment—how does visual acuity measured on an eye chart compare with visual function in common circumstances, such as reading a newspaper or recognizing a friend or loved one (Figure 1)?

*Based on a presentation by Dr Ho at a symposium held in conjunction with the Association for Research in Vision and Ophthalmology Annual Meeting in Fort Lauderdale, Florida, on May 5, 2007.

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The most commonly used tool to measure vision-related quality of life is the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25; available at the NEI Web site [www.nei.nih.gov]).¹ The NEI VFQ-25 is a patient-oriented assessment of the impact of vision problems on function; it is used for many common eye conditions. The NEI VFQ-25 has 25 questions in 3 sections: general health and vision, difficulty with activities, and responses to vision problems. A clinically meaningful change in this tool is at least 10 points, although smaller values also may be clinically relevant. The section on difficulty with activities includes 11 questions on the patient's ability to read ordinary print in newspapers; do work or hobbies that require seeing well up close; find something on a crowded shelf; read street signs or names of stores; descend stairs or step down from a curb in dim light or at night; notice objects off to the side while walking; see how people react to their comments; pick out and match clothes; visit with people in homes, at parties, or restaurants; see movies, plays, or sporting events; and drive (including driving at night and in difficult conditions). Note that these include near and distance activities, in addition to vision-specific dependency. Issues such as ability to drive are paramount to elderly patients because of the association with independent living. Studies have shown higher rates of depression in patients with more severe vision loss from AMD, especially with regard to valued activities.²⁻⁴

The NEI VFQ-25 was used in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) trials. To evaluate the results, it is important to remember which eye is being treated. In some participants, the better-seeing eye was treated with the study drug, which would magnify the response to treatment and effect on quality of life. On the other hand, participants whose worse-seeing eye was treated (ie, the other eye was 20/25) would be expected to experience a lesser benefit with the study drug. In the MARINA study, less than 50% of the study eyes were the better-seeing eye at baseline (eg, study eye 20/80, nonstudy eye 20/200), thus the effect on quality of life might be muted. (The percentage of patients being treated in the better-seeing eye were

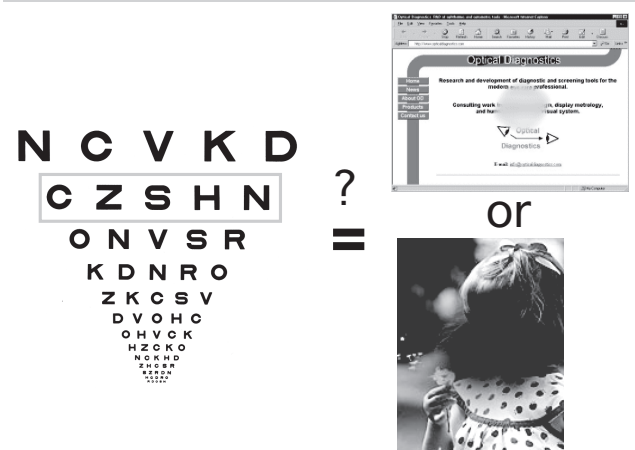
37% [sham], 43% [ranibizumab 0.3 mg], and 44% [ranibizumab 0.5 mg].) The results show significant improvements in quality of life with both ranibizumab doses, irrespective of whether the better- or worse-seeing eye was treated (Figures 2–4),⁵ although the degree of improvement is less for those with the worse-seeing eye treated.

Thus, even when the worse-seeing eye is treated, ranibizumab is more likely to change patients' perceptions regarding near activities (eg, finding something on a shelf), distance activities (eg, descending dimly lit stairs), and vision-specific dependency (eg, needing help from others to write a check), all of which are tangible and important benefits to patients with AMD. Moreover, when healthcare resources are limited, the choice of therapy may depend on not only evidence-based clinical outcomes but also validated tools for measuring quality of life.

COMMON QUESTIONS WITH AMD TREATMENT

Along with addressing patient expectations of treatment, the ophthalmologist should be prepared to address the expectations and questions from referring

Figure 1. How Does Visual Acuity on an Eye Chart Compare to Visual Function?



A clinically significant change in visual acuity score (as measured by lines or letter on an eye chart) may not translate into functionally significant changes for patients in their daily lives (eg, reading or recognizing someone). Images reprinted with permission from <http://www.allaboutvision.com/conditions/amd.htm> and <http://www.opticaldiagnostics.com/products/mds/screenshots.html>.

physicians. Below is a list of some of the most common questions I encounter regarding AMD treatment and the types of answers I give.

WILL I IMPROVE WITH RANIBIZUMAB TREATMENT?

Although the results from the ranibizumab studies are exciting and appear to present a new direction in AMD management, it is important to remember that most patients will not see a large improvement in visual acuity (eg, 3 lines of vision or approximately 15 letters). In the MARINA and ANCHOR studies, only approximately 33% of patients had visual acuity improvement of 3 lines or more, as compared to the sham treatment group, in which only 6% had this level of vision improvement.⁴ However, treating is far better than not treating.

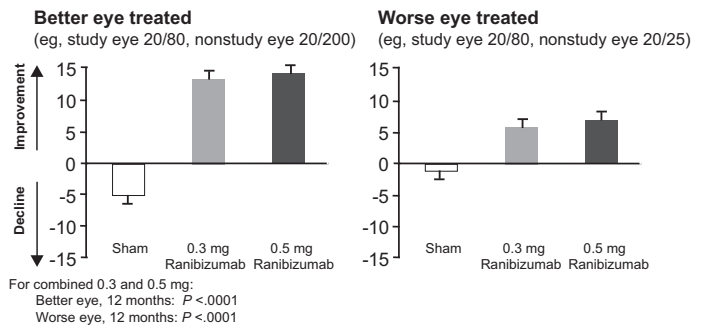
WILL MY VISION GET WORSE WITH TREATMENT?

Most patients' vision will not get worse with treatment, but some will. Not all patients respond to anti-VEGF treatment. Therefore, although it is possible that vision will worsen, the chances of that happening are much less if the eye is treated. Note that this is different from saying that most people will improve. In fact, a 4-letter gain may not be considered improvement and even a 9-letter gain may not be improvement if baseline vision is 20/160. Also, some patients will develop retinal pigment epithelial tears and some patients (not uncommonly) will not have the resources and/or time (eg, asking their adult child to take off a day of work every few weeks to bring them in for an office visit) to follow through with the treatment protocol.

IS THERE ANY RISK TO ME?

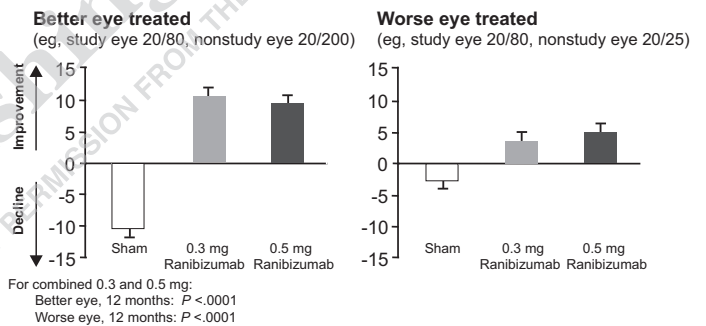
As with any medical treatment, there is always an element of risk; the risk is not zero. The major risk of concern, endophthalmitis with injection into the eye, is rare (up to 1.3% in clinical trials).⁶⁻⁸ Less serious but still important risks include subconjunctival hemorrhage, scratchy eyes, or even a corneal abrasion, of which patients should be made aware. There have been higher incidences of systemic adverse events with intravenous anti-VEGF treatment (eg, hypertension and risk of myocardial infarction or stroke), but they were not statistically significant. Of course, these will have to be monitored carefully as these drugs are introduced into a wider patient population, outside of a clinical trial setting.

Figure 2. Mean Change in Near Activities from NEI VFQ-25 at Month 12: Results from the MARINA Study



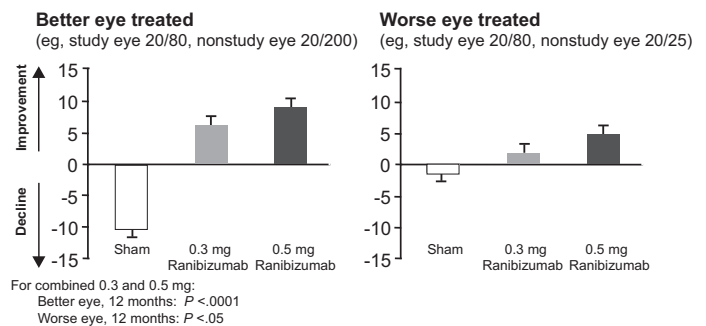
MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25. Reprinted with permission from Genentech, Inc.⁵

Figure 3. Mean Change in Distance Activities from NEI VFQ-25 at Month 12: Results from the MARINA Study



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Figure 4. Mean Change in Dependency from NEI VFQ-25 at Month 12: Results from the MARINA Study



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HOW MANY TIMES WILL I HAVE TO COME BACK TO THE OFFICE?

Unfortunately, the answer is “a lot.” Until we are able to answer the questions of treatment and monitoring frequency, as put forth by Dr Sadda in this monograph, we are unable to say with certainty how often we will need to treat and if a treatment will be warranted at each visit. However, even if patients with AMD do not receive anti-VEGF treatment, they will still need to be monitored frequently.

HOW MUCH WILL IT COST?

If the patient is using ranibizumab and has Medicare and secondary insurance, it usually costs nothing out of pocket. If the patient is insured and has a co-pay (or the Medicare secondary insurance does not cover the 20% difference), ranibizumab can be expensive for some patients (ie, \$414 every 4 to 6 weeks). If the patient has no insurance, there are financial assistance programs from all of the anti-VEGF treatment manufacturers, but not all patients are eligible or are approved. In some cases, the physician may choose to treat instead with bevacizumab, but there is clearly less evidence to support this, and certainly not level 1 evidence.

REMAINING QUESTIONS

Other questions remain for which we do not yet have answers, such as can we treat less often? If we switch to bevacizumab, what are the risks versus benefits? If we use combination therapies, can we reduce the number of treatments and visits, and can we actually achieve higher efficacy with similar safety?

THE ROLE OF COMBINATION THERAPY

Because AMD is a complex disease, a combination therapy will most likely be the ideal treatment. Augustin et al proposed that a combination of verteporfin photodynamic therapy (PDT), an anti-VEGF treatment, and an intravitreal steroid would be one such optimal combination therapy because the verteporfin PDT would eradicate existing CNV, the anti-VEGF treatment would attenuate inflammatory reactions to CNV eradication with the corresponding upregulation in VEGF, and the steroid would limit further VEGF upregulation.⁹ In their recently published case series, they chose verteporfin PDT, bevacizumab (because ranibizumab was not yet approved

by any regulatory agency for use in humans), and intravitreal dexamethasone (for its multiple pharmacologic effects [ie, more rapidly cleared from the vitreous and has antifibrotic, in addition to antiproliferative and antimigration, properties on vascular smooth muscle cells] and availability as a solution). In this study, 104 patients with neovascular lesions (22.1% predominantly classic, 38.5% minimally classic, and 39.4% occult) received a single cycle of verteporfin PDT at a reduced (84%) fluence, bevacizumab, and dexamethasone. A small number of patients ($n = 18$) received 1 additional bevacizumab injection at a mean of 15 weeks after the first cycle and 5 patients received a second triple therapy cycle. The mean follow-up period was 40 weeks (range, 22–60 weeks). The results showed a mean increase of 1.8 lines in visual acuity ($P < .01$). A total of 39.4% gained 3 or more lines, whereas 3.8% lost 3 or more lines. The mean follow-up visual acuity score was 20/85 versus 20/126 at baseline ($P < .01$). In fact, 28.8% of patients had a score of 20/40 or better at last follow-up. Also, the mean retinal thickness decreased by 182 μm ($P < .01$). Therefore, the efficacy of triple therapy appears to be noninferior to anti-VEGF monotherapy, but this is a preliminary case series.⁹ Larger, randomized trials of combination therapies are warranted and several are currently in progress—the DENALI and LUV studies (PDT at standard and half-fluence + ranibizumab), the MONT BLANC study (PDT at standard fluence + ranibizumab), the RADICAL study (PDT + ranibizumab + dexamethasone), VERITAS (verteporfin + intravitreal triamcinolone acetonide), and the BRIDGE study (anecortave acetate + ranibizumab).

CONCLUSIONS

Physicians can expect most patients to maintain or improve visual acuity, with an approximately 33% chance of 3-line improvement. For patients, quality of life is a more tangible benefit than visual acuity scores, and the ranibizumab studies show that quality-of-life measures improve with this treatment, even if the worse-seeing eye is treated. Combination therapy, although currently unproven in terms of enhanced efficacy or safety, may be a more reasonable approach to this disease in the future, particularly when patients and lesions are recalcitrant.

REFERENCES

1. Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol*. 2001;119:1050-1058.
2. Lotery AJ, Xu X, Zlatava G, Loftus J. Burden of illness, visual impairment, and health resource utilisation of patients with neovascular age-related macular degeneration: results from the United Kingdom cohort of a five-country cross-sectional study. *Br J Ophthalmol*. 2007;epub.
3. Augustin A, Sahel JA, Bandello F, et al. Anxiety and depression prevalence rates in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2007;48:1498-1503.
4. Rovner BW, Casten RJ, Hegel MT, et al. Dissatisfaction with performance of valued activities predicts depression in age-related macular degeneration. *Int J Geriatr Psychiatry*. 2007;epub.
5. Data on file. Genentech, Inc.; South San Francisco, Calif.
6. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-1431.
7. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432-1444.
8. Gragoudas ES, Adamis AP, Cunningham ET, et al. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med*. 2004;351:2805-2816.
9. Augustin AJ, Puls S, Offermann I. Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab, and dexamethasone. *Retina*. 2007;27:133-140.

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