

## THE CURRENT STATE OF THERAPY FOR AGE-RELATED MACULAR DEGENERATION\*

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### ABSTRACT

Over the past decade, treatment of neovascular age-related macular degeneration has evolved from overall retinal ablation to more targeted and retinal-sparing therapy, beginning with the advent of photodynamic therapy and continuing with the development of inhibitors to vascular endothelial growth factor (VEGF). This article summarizes the key clinical trials with photodynamic and anti-VEGF therapies to provide insight into and a framework around which we can choose the optimal treatments (including dosing) for our patients. Our patients now have more choices than ever with a greater chance of not only avoiding vision loss but also perhaps regaining some visual function in a proportion of patients. Ongoing and future studies should help us to answer the questions of optimal dosing and which patient characteristics may predict better outcomes.

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It has been an interesting and important journey over the past decade to our current state of treating neovascular age-related macular degeneration (AMD). We have evolved from overall ablation of the retina to more targeted and retinal-sparing therapy. This change began with the advent of photodynamic therapy, and continued with the development of inhibitors to vascular endothelial growth factor (VEGF), with which we can now maintain visual acuity without harming the retina. The most recent development in anti-VEGF therapies, ranibizumab, suggests that we cannot only maintain visual acuity in the vast majority of patients, but also improve visual acuity in a significant proportion of patients. This article will summarize the key clinical trials with photodynamic and anti-VEGF therapies to provide insight into and a framework around which we can choose the optimal treatments (including dosing) for our patients.

### PHOTODYNAMIC THERAPY

The Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Investigation consisted of 2 multicenter, double-masked, placebo-controlled, randomized trials comparing the efficacy and safety of verteporfin to placebo regarding the risk of vision loss in patients with subfoveal choroidal neovascularization (CNV) caused by AMD.<sup>1</sup> After 1 year of follow-up, fewer randomized participants who received verteporfin treatment lost at least 15 letters (approximately 3 lines of visual acuity; 39% vs 54%;  $P < .001$ ; for all TAP-enrolled participants).<sup>1</sup> The treatment benefits were maintained at 2 years (46% vs 62%;  $P < .001$ ).<sup>2</sup> Even greater benefit was observed in those with predominantly classic

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lesions—the percentage of participants who lost at least 3 letters of visual acuity were 38% versus 61% (verteporfin vs placebo;  $P < .001$ ; year 1) and 41% versus 69% ( $P < .001$ ; year 2), respectively.<sup>1,2</sup>

In the Verteporfin in Photodynamic Therapy (VIP) Trial, participants with either subfoveal CNV due to AMD or pathologic myopia were enrolled; however, the analyses of each group were published separately. The participants with AMD received verteporfin (or placebo) in year 1, with follow-up examinations every 3 months; retreatment with either verteporfin or placebo (as assigned at baseline) was applied to areas of fluorescein leakage if present. During year 2, follow-up examinations continued every 3 months and retreatment with either verteporfin or placebo (as assigned at baseline) was applied to areas of fluorescein leakage if present. After 1 year, the primary outcome time point, there was no statistically significant differences with respect to the percentage of eyes avoiding 15-letter loss or more (51% verteporfin vs 54% placebo lost at least 15 letters;  $P = .52$ ). After 2 years of follow-up, benefits with verteporfin were again observed compared to placebo—15-letter loss or more relative to baseline (54% vs 67%, verteporfin vs placebo;  $P = .023$ ); 30-letter loss or more relative to baseline (30% vs 47%, verteporfin vs placebo;  $P = .001$ ).<sup>3</sup>

As reviewed by Virgili et al, the TAP Investigation included two well-designed studies, with clear primary endpoints and more than sufficient enrollment to achieve statistical power.<sup>4</sup> The TAP Investigation, in conjunction with other verteporfin clinical trials, “provided a strong rationale for the benefits of verteporfin therapy in patients with subfoveal CNV and 1 of 2 lesion compositions—predominantly classic CNV or occult with no classic CNV with evidence of recent disease progression, although the strength of the evidence is not as great for this latter situation.”<sup>4</sup>

#### ANTI-VEGF THERAPIES: PEGAPTANIB

Two concurrent, randomized, double-blind, multicenter, dose-ranging, sham-controlled studies were conducted in a total of 1186 randomized study participants to assess the safety and efficacy of pegaptanib; both studies were analyzed together (the VEGF Inhibition Study in Ocular Neovascularization trial). Intravitreal injections of pegaptanib (0.3 mg, 1.0 mg, or 3.0 mg) were administered to 1 eye per participant every 6 weeks over a period of 48 weeks. After 1 year,

70% of the pegaptanib-treated participants ( $n = 296$ ) versus 55% of the sham-treated patients ( $n = 294$ ) lost fewer than 15 letters of visual acuity ( $P < .001$ ) with the 0.3-mg dose, with no dose response with the other doses.<sup>5</sup> The risk of losing 30 or more letters was also reduced with pegaptanib treatment (22% vs 10%, placebo vs pegaptanib 0.3 mg;  $P < .001$ ).<sup>5</sup>

Of initial concern with pegaptanib was the safety profile, as this was the first time patients with AMD were subject to repeated intravitreal injections. After the first year of the study, 12 (1.3%) participants had endophthalmitis, 5 (0.9%) experienced traumatic injury to the lens, and 6 (0.7%) experienced retinal detachment. However, only 2 participants (1 patient with endophthalmitis and 1 patient with traumatic injury to the lens; 0.2%) had resultant severe loss of visual acuity (loss of  $\geq 30$  letters) as a result of these adverse events.<sup>5</sup> It should also be noted that in the second year of the study, more meticulous attention was likely given to the injection protocol (ie, lid speculum use, drape use, and povidone-iodine solution 5% flush) and fewer events were noted (Data on file with Pfizer Inc). Also, in 8 of 12 endophthalmitis (66%) patients, the endophthalmitis was associated with protocol violations (eg, active ocular surface infection present and no eyelid speculum used).<sup>5</sup>

#### ANTI-VEGF THERAPIES: RANIBIZUMAB

The approval of ranibizumab by the US Food and Drug Administration was based on 2 pivotal trials—the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study.

##### THE MARINA STUDY

The MARINA study was a 2-year, multicenter, double-blind, sham-controlled study in which 716 study participants were randomized to receive 24 monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) or sham injections. Participants could enroll in the study if they had minimally classic (or occult with no classic) CNV with presumed recent disease progression (eg, evidence of blood, lipid, or recent drop in visual

acuity, which was confirmed angiographically).<sup>7</sup>

The results at year 1 showed notable differences between treatment and sham in both percentage of participants losing fewer than 15 letters and the primary endpoint (95% 0.5 mg ranibizumab; 95% 0.3 mg ranibizumab; 62% sham). Moreover, visual acuity improved in many more participants than noted in any previous neovascular AMD trials—the percentage of participants gaining at least 15 letters was 34% (0.5 mg), 25% (0.3 mg), and 5% (sham). The results were maintained for year 2—percentage of participants losing fewer than 15 letters was 90%, 92%, and 53%, respectively, and the percentage of participants gaining at least 15 letters was 33%, 26%, and 4%, respectively. The mean change in visual acuity at year 1 was +7.2 letters for 0.5 mg ranibizumab, +5.9 letters for 0.3 mg ranibizumab, and -9.1 letters for sham. By year 2, the respective mean changes were +6.6, +5.4, and -14.9.<sup>7</sup>

The anatomic correlates of efficacy also illustrated benefit with ranibizumab treatment, at both doses. The mean area of leakage among the 3 groups was comparable at baseline (3.5 disc areas). By month 12, those values had changed to 1.6 (0.5 mg ranibizumab) and 4.7 (sham); by month 24, they were 1.3 and 4.3, respectively. The results for 0.3 mg ranibizumab were comparable.

Since the publication of the MARINA results, subanalyses were performed to determine whether certain baseline characteristics might influence the efficacy of ranibizumab. In fact, the beneficial effect of ranibizumab over sham was consistently observed across all baseline subanalyses, including age, gender, baseline visual acuity, and baseline choroidal lesion area with regard to the primary endpoint at month 24.<sup>8</sup>

Ocular adverse events were as follows. At year 1, sham participants experienced no adverse events, whereas participants in the ranibizumab group (0.5 mg) experienced culture-negative endophthalmitis (0.8%), uveitis (0.4%), retinal tear (0.4%), vitreous hemorrhage (0.4%), and lens damage (0.4%). By year 2, 0.4% of sham-treated participants experienced rhegmatogenous retinal detachment (vs 0% in the ranibizumab group) and 0.8% experienced vitreous hemorrhage (vs 0.4% in the ranibizumab group). Ranibizumab-treated participants also reported culture-negative endophthalmitis (1.3%), uveitis (1.3%), retinal tear (0.4%), and lens damage (0.4%) at year 2.<sup>7,8</sup>

Because of the previous experience with bevacizumab, systemic safety was also of concern. In fact, the rates of hypertension, change in systolic/diastolic blood

pressure, and rate of myocardial infarction were comparable between sham and ranibizumab-treated participants, at both year 1 and year 2. Rates of cardiovascular accidents were slightly higher in the ranibizumab group (1.3% vs 0.4%, year 1; 2.5% vs 0.8%, year 2). Death rates were also comparable between the 2 groups at year 1 and year 2.<sup>7,8</sup>

#### THE ANCHOR STUDY

The ANCHOR study was a 2-year, multicenter, double-blind study, in which 423 study participants with predominantly classic CNV (confirmed angiographically) were randomized to receive 12 monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) plus sham verteporfin therapy or monthly sham injections plus active verteporfin therapy. Thus, ranibizumab was directly compared to photodynamic therapy with verteporfin.<sup>9</sup>

The results showed similar degrees of benefit as in the MARINA study. At month 12, 96.4% of participants treated with 0.5 mg ranibizumab lost fewer than 15 letters compared to 64.3% of the sham-treated participants. Conversely, 40.3% of the ranibizumab-treated participants gained at least 15 letters compared to 5.6% of the sham-treated participants. This resulted in a 20.8-letter difference in mean visual acuity change from baseline by month 12 ( $P < .001$ ; +11.3 letters vs -9.5 letters).<sup>9</sup> And, as with the MARINA study, the mean area of leakage was greater in the verteporfin-treated group compared to the ranibizumab groups. Moreover, no particular subgroup appeared to influence the primary efficacy outcome, and ranibizumab was effective across subgroups of age, gender, baseline visual acuity, and baseline vision size.<sup>9</sup>

Analysis of ocular adverse events revealed small differences between the ranibizumab and verteporfin groups. Rates of rhegmatogenous retinal detachment were 0.7% with verteporfin versus 0% with ranibizumab, whereas rates of culture-positive and culture-not-done endophthalmitis were 0.7% each in the ranibizumab group versus 0% in the verteporfin group. Uveitis occurred more frequently with ranibizumab than verteporfin (0.7% vs 0%).<sup>9</sup> Systemically, rates of hypertension were slightly higher with verteporfin versus ranibizumab (8.4% vs 6.4%), whereas changes in systolic/diastolic blood pressure were comparable and minimal. Myocardial infarction rates were slightly higher with ranibizumab (2.1% vs 0.7%); rates of cardiovascular accidents were compara-

ble (0.7% each). Death rates were also comparable (1.3% vs 1.4%, verteporfin vs ranibizumab).<sup>9</sup>

#### THE PIER STUDY

The PIER study represents a large randomized, double-masked, sham-controlled study of 0.3 and 0.5 mg ranibizumab in 184 patients with subfoveal CNV, with or without a classic component, most of whom had classic lesions. The PIER study examined whether reduced dosing would have an effect on visual acuity outcomes. In the PIER study, study participants were injected or received sham monthly for 3 months, then every 3 months up to 12 months.

The results are not yet published; however, preliminary reports show a 16.1-letter difference in mean visual acuity change from baseline after 12 months (-0.2 0.5 mg ranibizumab vs -16.3 sham;  $P < .0001$ ). In terms of comparable outcomes to MARINA and ANCHOR (ie, percentage of participants losing fewer than 15 letters and gaining at least 15 letters), the results show 90% of 0.5-mg ranibizumab participants lost fewer than 15 letters versus 49% of sham-treated patients. However, only 13% and 10% of ranibizumab- (0.5 mg) and sham-treated participants, respectively, gained at least 15 letters. Mean area of leakage decreased from 4.0 to 2.7 in the 0.5 mg ranibizumab group, but increased from 4.2 to 5.6 in the sham-treated group. To date, there have been no ocular adverse events with regard to endophthalmitis, uveitis, rhegmatogenous retinal detachment, retinal tear, vitreous hemorrhage, or lens damage. Rates of adverse events have been comparable between ranibizumab- and sham-treated groups (Data on file with Genentech).

However, it is important to note that there are other common adverse events with ranibizumab therapy, which may not be characterized as “serious” but of which patients should be made aware. These include superficial punctate keratopathy or potential corneal abrasion resulting from use of the povidone-iodine or from insertion of the lid speculum. Also, because ranibizumab involves a transconjunctival injection, patients may experience subconjunctival hemorrhage, which can be problematic if the patient is concerned about their appearance in the days immediately following the injection (eg, participating in an important photograph or giving a presentation). If patients are aware of these adverse events, they can adjust their schedules accordingly.

Overall, the initial PIER results suggest that reduced-interval dosing offers better visual outcomes

than the natural disease progression with AMD. However, reduced dosing was not compared directly with monthly injections, thus it is not possible to yet comment on which dosing regimen is preferred.

#### THE SAILOR STUDY

Lastly, the SAILOR study is an ongoing phase IV, open-label study of ranibizumab 0.3 versus 0.5 mg, administered every month and for 3 injections, and then as needed. An analysis after 230 days showed that the risk of cardiovascular accidents was higher with the 0.5-mg versus 0.3-mg dose (1.2% vs 0.3%;  $P = .02$ ); however, age-matched controls had an average cardiovascular accident rate of 3%. Study participants with a history of prior cardiovascular accident receiving ranibizumab were at higher risk of an additional cardiovascular accident. Further results from a more long-term analysis are needed.

#### CONCLUSIONS

The clinical trials of photodynamic therapy with verteporfin and the anti-VEGF therapies are an important foundation for optimal treatment of AMD. Our patients now have more choices than ever with a greater chance of not only avoiding vision loss but also a greater chance of regaining some visual function. Clinicians must discuss the risks and benefits of each treatment with their patients, including the “not serious” but bothersome side effects of some of these treatments. Ongoing and future studies should help us to answer the questions of optimal dosing and which patient characteristics may predict better outcomes.

#### Q&A HIGHLIGHTS

**Question: For the study participants in the MARINA and ANCHOR analyses who had not shown improvement of 15 letters or more at month 4 but improved by that amount by month 12, do we know how many of them may have shifted by only 2 or 3 letters? Or, had most of them shifted by more than 5 letters?**

*Dr Lim:* That’s a good point, as potentially it might be “noise.” I don’t know which patients shifted by only a few letters.

**Question: What were the optical coherence tomography (OCT) characteristics of the study partici-**

**pants who did not increase by 15 letters or more by 4 months but did so sometime thereafter?**

*Dr Lim:* That's a great question. There is a subgroup analysis based on whether study participants were leaking or not at month 4 and if that status continued to month 12. If study participants had no leakage from CNV at month 4, they had a better chance of increasing by 15 letters or more at month 12 than if they had leakage at month 4 (Data on file with Genentech).

*Dr Bressler:* I believe that was using fluorescein angiography; very few people in the MARINA or ANCHOR trials had OCT. So, we have limited OCT data from these trials. We know it works, we know it helps visual acuity, but Dr Sadda will discuss how to use OCT.

**Question: If you have a patient who has already lost vision in 1 eye due to AMD, and if they have dry AMD in the second eye, would you consider treating them before they have evidence of wet AMD, in light of the success of ranibizumab?**

*Dr Lim:* That is an interesting question, as it addresses the issue of prophylactic therapies for high-risk patients with AMD (ie, potentially a patient could have at least 50% risk of moderate visual loss using the AREDS [Age-Related Eye Disease Study] risk classification). The clinical trials that have been completed using ranibizumab were only on eyes that had active, subfoveal, wet CNV. If you take an eye that has, for example, 50% risk and subject it to monthly injections, we don't really know how many monthly injections you need to do. How many eyes would you unnecessarily need to treat to save the eyes that would go on to becoming wet? There are prophylactic studies using other drugs with potentially safer treatment regimens than monthly intravitreal injection of ranibizumab. One study that gets to the heart of your question is the AARRT study (Anecortave Acetate Risk Reduction Trial), which is looking at just that. Another study looking at reducing the risk is the AREDS-2 study ([www.clinicaltrials.gov](http://www.clinicaltrials.gov); NCT00345176), which is looking at lutein, zeaxanthin, and fish oil (omega-3 fatty acid) supplements to see if, in high-risk eyes, we can decrease the percentage of eyes that go on to visual loss with prophylactic treatments compared to the natural course.

*Dr Bressler:* At least 50% of patients, in that situation, do not go on to neovascularization in 5 years. We would need definitive evidence that it really reduces the risk of initiating a neovascular process that could cause

vision loss. Maybe it would just prevent the neovascular cases that aren't a problem. For example, maybe it prevents the ones that are occult with no classic CNV that stay 20/20 for years. We would need to know the answer to that because we're talking about doing 60 injections over 5 years, and in half of the eyes it wouldn't be needed. We would need pretty strong evidence to support that, let alone the expense and the inconvenience of office visits to have the injections done. Nevertheless, prevention is definitely a worthy and important goal in this condition. If anecortave acetate, or some other medication, could be given infrequently and shown to prevent it, that would be important.

*Dr Lim:* Also, anecortave is given as a juxtasclear posterior sub-Tenon capsule injection, thus you're not actually injecting into the eye, and it only has to be injected every 6 months. Therefore, it's potentially a bit safer than intravitreal injections.

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