

Steroid Implant Alone and as an Adjunct to Anti-VEGF for CNV in AMD

The extended-release device alone provided clinically and statistically significant improvement in central retinal thickness.

BY MICHAEL A. SINGER, MD

Choroidal neovascularization (CNV) is a common and potentially vision-threatening symptom of advanced age-related macular degeneration (AMD).^{1,2} Therapies for CNV secondary to AMD have focused on addressing vascular endothelial growth factor (VEGF) using antiangiogenic therapy.^{3,4} Anti-VEGF therapy with ranibizumab (Lucentis, Genentech) has been shown in the pivotal clinical trials ANCHOR⁵ and MARINA⁶ to be highly effective in preventing visual acuity loss and improving visual function and anatomy in patients with neovascular AMD. In addition, the HORIZON study⁷ demonstrated the long term safety of ranibizumab injections and the need for close follow-up to prevent loss of vision. Recently, the VIEW 1 and VIEW 2 studies demonstrated that aflibercept also shows efficacy in improving vision and preventing visual loss.⁸⁻¹⁰

As our experience in the 6 years since the regulatory approval of ranibizumab has shown, however, the need for monthly anti-VEGF injections can place significant burdens on patients, retina practices, and the health care system.¹¹ The 1-year results of the CATT study¹² suggested the equivalence of monthly injections to an as needed (prn) therapy regimen. However, patients still must be followed every month because it is unclear who will need an additional injection and when. In fact, when an anti-VEGF injection

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is given, it is currently unknown how long that shot will last in an individual and how effective that single injection will be in reducing macular edema. A strategy that could reduce the frequency needed for anti-VEGF treatment and increase its predictability of effect would be desirable.

It is known that in addition to angiogenic mediators, inflammatory factors also play a role in the pathology of neovascular AMD. Combination strategies that address the inflammatory component of the disease with the aim of reducing the frequency of anti-VEGF injections are under investigation.⁴ Among these strategies is a triple combination of intravitreal injection of the corticosteroid triamcinolone acetonide plus photodynamic therapy and anti-VEGF therapy.¹³ Some studies seem to indicate that this type of therapy may be effective in treating neovascular AMD and reducing the frequency of anti-VEGF treatments needed.^{13,14}

EXTENDED-RELEASE IMPLANT

Ozurdex (dexamethasone intravitreal implant, Allergan) is a biodegradable implant that can be injected into the posterior chamber. It gradually releases 0.7 mg dexamethasone into the back of the eye for a sustained period of time. In the United States, the implant is indicated for treatment of macular edema following retinal vein occlusion and noninfectious uveitis involving the posterior segment.¹⁵

A randomized controlled study evaluating the use of the dexamethasone implant in combination with ranibizumab in patients with treatment-resistant neovascular AMD found that the implant significantly delayed or reduced the need for repeated ranibizumab injection. The treatment also demonstrated an acceptable safety profile.¹⁶

OPEN-LABEL STUDY

The results of a 26-week multicenter open-label trial, performed to evaluate the dexamethasone implant 0.7 mg as adjunctive therapy to intravitreal ranibizumab in treatment-naïve subjects with subfoveal CNV secondary to AMD were recently presented.¹⁷

Patients enrolled in the study were 50 years of age or greater with active subfoveal CNV secondary to AMD in at least 1 eye. Inclusion in the study required a total lesion size of 12 Macular Photocoagulation Study disc areas (approximately 30.48 mm²) or less, a 1-mm central retinal subfield mean thickness of 300 µm or greater as assessed by optical coherence tomography (OCT), and best corrected visual acuity (BCVA) of 19 to 75 letters on the ETDRS chart. Patients with a history of other treatment for CNV; subfoveal scarring, fibrosis, or atrophy; CNV for any reason other than AMD; glaucoma or a history of intraocular pressure (IOP) elevation in response to corticosteroids were excluded.

All eyes received the dexamethasone implant at the baseline visit on day 1. No other treatments for CNV other than ranibizumab were allowed after day 1. At the week 2 study visit, eyes were eligible for treatment with ranibizumab 0.5 mg if BCVA had dropped 5 letters or more from the day 1 visit. Eyes not eligible for ranibizumab at week 2 could be treated with ranibizumab at week 3 if BCVA had dropped by 5 letters or more from the day 1 visit. Study visits continued every 4 weeks starting with week 4. At weeks 4 to 22, ranibizumab 0.5 mg could be given at the discretion of the investigator.

The primary efficacy endpoint was change from baseline central retinal thickness (CRT) at week 4. Other efficacy measures included changes in BCVA and angio-

In patients with treatment-resistant neovascular AMD ... the implant significantly delayed or reduced the need for repeated ranibizumab injection.

graphic macular leakage, as well as the total number of ranibizumab injections administered during the 26-week study period. Safety measures included adverse events and IOP elevation.

RESULTS

The majority of the patients (54.5%) were white, but almost half (45.5%) were Asian because the study was performed in both the United States and Asia. Mean patient age was 72 (range, 51–94) years, and mean duration of CNV was a little more than 1 month (34.8 days; range, 0–375). The type of AMD was classic-only in 3 (6.8%) eyes, predominantly classic in 7 (15.9%), minimally classic in 16 (36.4%), and occult-only in 18 (40.9%). Baseline CRT was 360.9 µm, and baseline BCVA was 46.5 letters.

Treatment with the dexamethasone implant alone resulted in statistically significant decreases from baseline in CRT at each weekly visit, starting at week 1 (40.3 ± 66.3 µm, $P < .001$ vs baseline) and continuing through the primary time point at week 4 (62.0 ± 78.7 µm, $P < .001$ vs baseline). (For eyes treated with ranibizumab before week 4, the CRT prior to the injection was carried forward through week 4 before the change from baseline was calculated.)

With the addition of ranibizumab as needed (prn) at week 4, the reduction in CRT was even more pronounced, reaching 124.6 ± 82.0 µm ($P < .001$ vs baseline) at week 8, and significant reduction from baseline was maintained at every time point through the end of the study at week 26 (133.7 ± 77.4 µm, $P < .001$ vs baseline).

Improvement in BCVA during the first 4 weeks was not statistically significant with the dexamethasone implant alone. A statistically significant increase in mean BCVA was first seen at week 8, and statistically significant increases were maintained through the end of the study at week 26. The percentage of eyes achieving at least a 15-letter (3-line) improvement from baseline BCVA was 4.5% at week 4, 11.4% at week 8, 20.5% (the peak effect) at week 22, and 15.9% at week 26.

The percentage of patients with leakage on fluorescein angiography (FA) decreased from 100% at base-

line to 83.7% at week 4 and 76.7% at week 26. The percentage of patients with a 10% or greater reduction in leakage from baseline was 39.5% at week 4 and 74.4% at week 26. Only 1 patient had a 10% or greater increase from baseline at week 4, and 3 had such an increase at week 26.

Regarding the number of ranibizumab injections given, it is notable that approximately 45% of patients needed 3 or fewer treatments during the course of the study to achieve these results, and approximately 20% needed 1 treatment or fewer. Before the week 4 endpoint, 7 patients (16.3%) received rescue ranibizumab. Over the course of the study, 3 (6.8%) patients received the maximum possible number of injections (6), and 16 (36.4%) received 5 injections.

The most common ocular adverse events included conjunctival hemorrhage, IOP increase, conjunctival edema, and dry eye. There was 1 case of endophthalmitis, which resolved with treatment. Of 3 patients (6.8%) with IOP elevation, all were easily controlled with drops. No filtering surgery or laser trabeculoplasty were performed. One person was discontinued from the study due to aspiration pneumonia unrelated to the study treatment.

DISCUSSION AND CONCLUSIONS

This open-label study provides the first demonstration of a beneficial effect of the combination dexamethasone implant and ranibizumab in patients with untreated neovascular AMD. The use of dexamethasone implant alone resulted in statistically significant improvements in CRT from baseline as early as week 1 and continued through week 4. In addition, clinically significant improvements in BCVA and fluorescein leakage were seen with the implant alone.

With the addition of ranibizumab, statistically significant improvements in CRT, BCVA, and FA leakage were seen. Most patients (84%) did not need rescue ranibizumab before 4 weeks. Over the course of 26 weeks, only 3 of the 44 patients enrolled (6.8%) received the maximum of 6 possible ranibizumab injections, and 16 (36.4%) received 5 injections. Almost half of the patients (45.5%) required 3 or fewer injections of ranibizumab over the study period to achieve these results, and 20.4% needed 1 injection or fewer.

In this study the implant as adjunctive therapy to ranibizumab was well tolerated, reduced macular edema, improved BCVA, and decreased the need for monthly injections of ranibizumab. Although these results are promising, this was a small, uncontrolled study, and further evaluation of combination therapy using dexamethasone implant as a treatment for CNV secondary to AMD is needed. ■

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