

Pegaptanib Treatment for CRVO

Significant improvement was seen on OCT among patients with macular edema following CRVO.

BY KARL G. CSAKY, MD, PhD

A randomized, dose-ranging, double-masked, parallel-group, sham-controlled, multicenter phase 2 trial evaluated the safety and efficacy of intravitreal pegaptanib (Macugen, OSI/Eyetech) in patients with macular edema following central retinal vein occlusion (CRVO) in a 1-year study.¹

The Macugen in CRVO Study included 98 patients at 38 centers in the United States, Europe, and Australia. Patients who met the inclusion criteria had a diagnosis of nonischemic CRVO by fluorescein angiography in the previous 6 months, macular edema present at baseline and day 1 of treatment, retinal thickness ≥ 250 μm by optical coherence tomography (OCT) at the center point, and visual acuity of 20/50 to 20/400. The study excluded patients who appeared to have ischemic CRVO, based on the presence of ocular neovascularization at baseline or an afferent pupillary defect. Although the visual acuity cutoff of 20/400 does not necessarily exclude ischemia, it does tend to mean that these patients' eyes were a little healthier than those who have severe ischemia.

Patients were assigned to pegaptanib doses of 0.3 mg ($n=33$), 1 mg ($n=33$), or a sham injection ($n=32$) every 6 weeks for 24 weeks. The patient groups were well balanced with regard to age and blood pressure, as well as baseline mean visual acuity (which was about 20/100) and mean centerpoint thickness (approximately 660 μm).

OCT FINDINGS

The OCT findings among patients treated with pegaptanib demonstrated a reduction in retinal thickening. The agent's pharmacokinetic effect is approximately 6 weeks, and OCT at 1 week showed the pegaptanib-treated patients had a reduction in centerpoint thickness of -267 μm (0.3-mg dose) and -210 μm (1-mg dose), compared with -5 μm (sham) ($P \leq .0001$). At

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3 weeks, the reduction was -329 μm in the 0.3-mg group and -198 μm in the 1-mg dose group, compared with -40 μm in the sham group ($P \leq .0001$). At 6 weeks, although the effect would be expected to be wearing off, there was still a reduction in thickness, albeit not as great as seen at 1 and 3 weeks; at 6 weeks the reduction was -169 μm , -114 μm , and -80 μm ; in the 0.3-mg, 1-mg, and sham groups, respectively ($P = \text{NS}$).

It is important to note that the natural history of vein occlusion is such that it improves on its own, unlike age-related macular degeneration (AMD). This underscores the importance of a control group in CRVO clinical trials. The fact that pegaptanib-treated patients showed dramatic improvement on OCT at 1 and 3 weeks with virtually no improvement in the sham group at these time points reveals that the agent had a dramatic effect.

Over 30 weeks, the reduction in centerpoint thickness on OCT continued, so that by the 30-week mark it was -273 μm (0.3 mg), -169 μm (1 mg), and -148 μm (sham).

When other OCT parameters were examined, we found that at week 3 the proportion of patients who had at least 200 μm of improvement was 72% in the 0.3-mg group, 43% in the 1-mg group, and only 14% in the sham group. As a group, the vast majority of patients did well with treatment, particularly with regard to the 0.3-mg dose.

This study tells us that CRVO patients treated with pegaptanib—based on findings of the OCT—do better than what can be expected with the natural history of the disease. It is fair to be somewhat critical, however, because the mean thickness at baseline was 680 μm and the subsequent mean change in the thickness was only -243 μm . These patients are not back to normal, but they are better than the natural history by approximately 100 μm .

VISUAL ACUITY

In general, OCT and visual acuity are not well correlated, especially in retinal vascular disease. In this study, at 30 weeks, the mean visual acuity improvement in pegaptanib-treated patients was +7.1 letters (0.3 mg) and +9.9 letters (1 mg), compared with a loss of 3.2 letters in the sham-assigned patients. Even though the natural history in CRVO by OCT criteria improved, visual acuity declined. In the treated patients in this trial, there was a statistically significant improvement in visual acuity.

The percentage of patients who lost ≥ 15 letters was 6% to 9% in the treated patients versus 31% in the sham group, showing that pegaptanib was protective against severe vision loss. In terms of visual acuity gains, 36% to 39% of treated patients improved by ≥ 15 letters compared with 28% in the control group.

SELECTIVE VS PAN-VEGF INHIBITION

In considering the rationale for choosing selective vs pan-vascular endothelial growth factor (VEGF) blockade, one must take into account two sites of potential toxicity. This potential toxicity, however, is difficult to assess due to a lack of sufficient clinical trial data on pegaptanib, bevacizumab (Avastin, Genentech), and ranibizumab (Lucentis, Genentech) in the treatment of retinovascular disorders. Significant ocular toxicity was not noted with these agents in clinical trials for the treatment of AMD. Bevacizumab has been used to treat CRVO and has been reported to be associated, in rare instances, with progressive retinal capillary dropout. It should be noted that the natural history of CRVO is that approximately 10% of patients will show progressive ischemia.

There is a theoretical reason why selective VEGF may be superior to pan-VEGF blockade in reducing photoreceptor cell death following ischemia, and there are animal data to support this.² Whether these animal data

translate into real benefit for our patients is unknown. In terms of systemic toxicity, several studies have demonstrated that all of these agents get out of the eye^{3,4} and into the systemic circulation, but we do not know the implications. If there are safety issues, they are subtle, and the number of patients who experience them is small. At Duke University, we are conducting a major Medicare database study to look at systemic toxicity with anti-VEGF agents. The AWARE (Analysis of Safety Outcomes with Anti-VEGF Treatment) trial is a landmark longitudinal study exploring the safety of VEGF therapies for the treatment of neovascular AMD and diabetic retinopathy (See *Retina Today*, May/June 2007 issue, page 32).

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I think the jury is still out on the advantage of selective vs pan-VEGF inhibition both in the treatment of retinal vascular disorders and in reducing systemic toxicity. We do know, however, that if there is a safety signal at all, it will be in a select group of patients and we have to decipher (1) whether there is a signal (2) and in what patients.

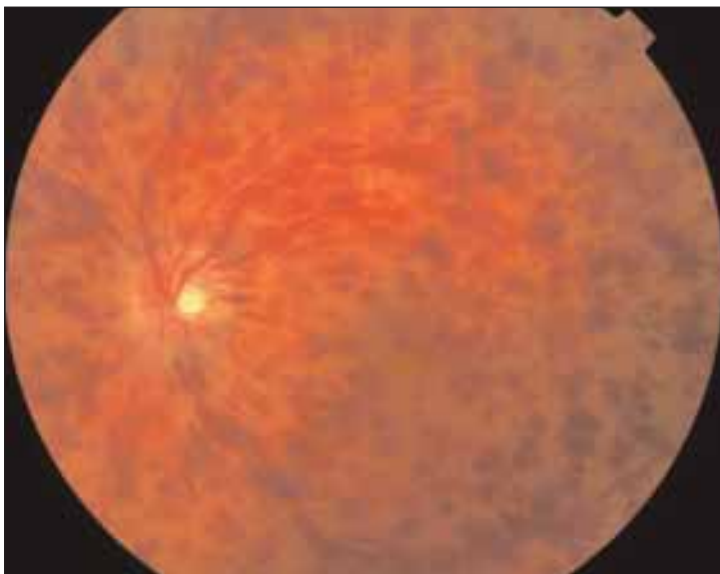


Figure 1. Color fundus photograph demonstrating typical fundus findings in CRVO of diffuse intraretinal hemorrhages, venous dilation and tortuosity and macular edema.

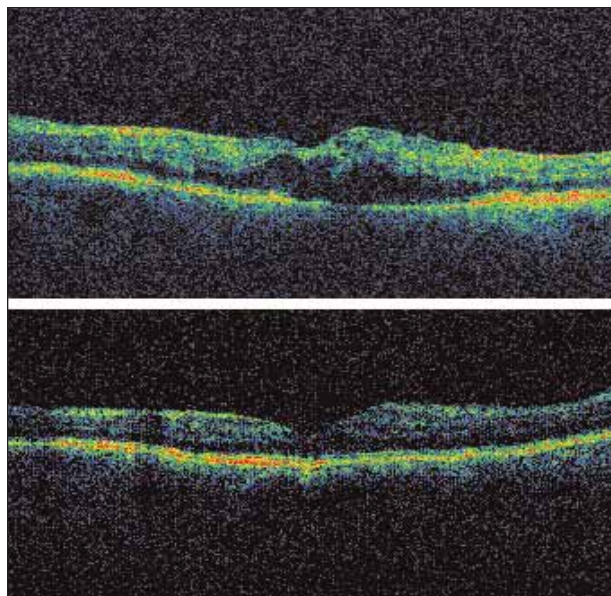


Figure 2. OCT images of a patient with diffuse macular edema secondary to a central retinal vein occlusion with central macular thickness of 575 μm (top) and 4 weeks after intravitreal pegaptanib injection showing dramatic resolution of the macular edema with a central macular thickness of 190 μm (bottom).

COMBINATION THERAPY

We have four treatments available for vein occlusion—selective VEGF inhibition, pan-VEGF inhibition, steroids, and laser—and I think it is fair to say that the best treatment is not going to be a single-agent approach. We must think about combination therapy. For example, we know that laser alone is not effective for CRVO, especially in patients 65 years of age or older.⁵ But will efficacy and durability of treatment be prolonged if one combines grid laser with other agents?

Retina specialists are trying to determine the best approach, and there are different schools of thought. For example, there may be a specific time course for the expression of VEGF in CRVO, and if we can block that for a certain amount of time, then that anti-VEGF treatment alone could be adequate. Short-term anti-VEGF alone does not appear to control most patients with neovascular AMD. It appears that the majority of patients with AMD do not reach a “burn-out” phase and we have to keep treating them. We do not yet have a handle on which patients with AMD do well with short-term anti-VEGF treatment or the reasons for this apparent durable response.

Some practitioners believe that, because the laser is the most durable treatment we have, perhaps we will always have to add laser at some point in the course of

treatment to prevent re-treatments. I do not believe specialists have yet fully embraced one approach or the other.

CLINICAL DECISIONS

At this time, when evaluating the approach for treatment in patients with CRVO, I take into account whether the patient is having disease in their first or second eye, how ischemic the retina appears, and I also consider all systemic issues. For patients in whom I am concerned about pan-VEGF blockade, I will usually use steroid treatment as my first approach, followed by bevacizumab if they are not responsive or have a steroid problem. If I think the patient is risking his only eye, has demonstrated progressive retinal ischemia, or has significant systemic vascular issues, I will use pegaptanib. My clinical experience mirrors what I reported from the clinical trial (Figures 1 and 2).

In my practice, we see a significant number of patients with vein occlusion and glaucoma, and in those patients we avoid steroids and use primarily an anti-VEGF agent. Then it becomes a question of how strongly the surgeon believes in the issue of pan-VEGF blockade vs a VEGF-isof orm-specific approach.

FINAL THOUGHTS

A major question in vein occlusion is that we really do not know to what degree VEGF is driving overall vision loss. We can get lost in the pegaptanib vs bevacizumab vs ranibizumab argument, but what we really need to know is what is the mechanism of vision loss in vein occlusion. We know it is not purely retinal thickness, as we have patients for whom we can improve anatomy and not improve vision. ■

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