

# Sustained Suppression of VEGF: Looking Forward and Looking Back



The results of the LADDER trial demonstrate a major step forward but introduce many questions.

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The results of the phase 2 LADDER trial testing the effects of sustained delivery of ranibizumab (Lucentis, Genentech) in patients with neovascular age-related macular degeneration (AMD) provide a glimpse into the future regarding how retinal and choroidal vascular diseases will be treated.<sup>1</sup> Although the technology evaluated in that trial—the Port Delivery System (PDS, Genentech), a surgically implanted, refillable reservoir—is interesting, the biological effects of eliminating the consequences of chronic overproduction of VEGF in the retinal pigment epithelium (RPE) and outer retina are astounding.

Intraocular injections of anti-VEGF agents have preserved functional vision and independence in many patients with neovascular AMD who, prior to the development of those agents, would almost certainly have become legally blind. The introduction of VEGF suppression for the treatment of wet AMD was thus one of the most important developments in ophthalmology over the past 20 years.<sup>2</sup>

However, in the future, I predict that we will use repeated intravitreal injections of anti-VEGF agents only as a brief therapeutic trial prior to administration of a more definitive long-term treatment.

## QUESTIONS, QUESTIONS

Sustained delivery of ranibizumab bestows quiescence to the turbulent macula of wet AMD patients, making an inherently unpredictable disease far more predictable. Although the results of LADDER clearly show that sustained suppression of VEGF

is a major step forward, the trial raised several questions.

The median time to first refill in the 100 mg/mL PDS arm was 18 months, which is remarkable, but the range was quite large. Why do some patients lose quiescence after 7 or 8 months while others maintain it for more than 2 years? Is the load of VEGF overexpression so different among patients, or is there disease modification in some patients, similar to what is seen in diabetic retinopathy, providing stabilization even when the delivery of ranibizumab has ceased or is very

## AT A GLANCE

- ▶ Results from the LADDER trial of sustained VEGF suppression provide a glimpse of the future of retinal and choroidal vascular disease treatment.
- ▶ But the trial results also raise questions regarding why patients responded to the treatment in varied ways.
- ▶ Other questions to be addressed include whether fluid in the macula will remain the most salient biomarker for disease activity.

**“WE ARE ON THE BRINK OF A PARADIGM SHIFT IN OUR MANAGEMENT OF NEOVASCULAR AMD AND RETINAL VASCULAR DISEASES, AND WE MUST BE OPEN TO NEW OBSERVATIONS... .”**

low? Is the biologic response to [continuous delivery of low levels of a VEGF antagonist fundamentally different from the response to the peaks and valleys resulting from repeated injections? Are there long-term negative consequences to sustained suppression of VEGF?

This last question harkens back to warnings from the CATT trial: “Because VEGF plays an important role in the normal function of the retina and the maintenance of the choriocapillaris by the RPE, therapies that block VEGF could have an effect on the development and progression of [geographic atrophy (GA)].” And, “These findings have important clinical implications and should be included in discussions with patients regarding the benefits and risks of the choice of treatment type and regimen. Although monthly injections may result in slightly better visual outcomes at 2 years, the increased risk of GA development may offset this benefit long term.”<sup>3</sup>

It was surprising that investigators involved in a clinical trial would assume causality from an association and make a recommendation that is counter to the primary outcome, which was change from baseline BCVA. The recommendation was not supported by the data from CATT nor the preponderance of evidence in the literature indicating that VEGF is not a survival factor for photoreceptors.<sup>4-6</sup> It appears likely that this warning was a contributor to the poor outcomes seen in CATT at 5 years<sup>7</sup> and to the undertreatment in clinical practice that has led to poor real-world outcomes.<sup>8</sup>

It is to be hoped that, as more data shed light on the long-term effects of sustained suppression of VEGF in neovascular AMD, we will exorcise the demons haunting us from past mistakes.

**WHAT ABOUT FLUID?**

As we have learned the negative consequences of undertreatment with anti-VEGF agents in patients with wet AMD, we have become intolerant of intraretinal and subretinal fluid. Fluid has been our biomarker for disease activity in patients receiving intermittent injections, but it is unclear whether it will have the same significance in patients receiving constant delivery of a lower dose of an anti-VEGF agent. Will fluid resorb more slowly than we are used to with bolus injections? Do small amounts of residual fluid suggest persistent disease activity that should be managed with supplemental injections, or is it consistent with quiescence and

should it therefore be observed? Will vision stability or lack thereof become a more important factor for interpretation of spectral-domain OCT findings?

**NEW LEARNINGS**

We are on the brink of a paradigm shift in our management of neovascular AMD and retinal vascular diseases, and we must be open to new observations and new learnings that will shape our treatment. These new learnings may stem from the answers to questions such as those presented here.

A refillable reservoir that slowly releases ranibizumab into the vitreous is the first foray into this new paradigm that will fundamentally change our approach to retinal and choroidal vascular diseases. Other approaches—such as the intravitreal injection of microparticles that slowly release a VEGF receptor antagonist into the eye and ocular gene transfer to provide sustained expression of a VEGF-neutralizing protein in the retina and RPE—are being investigated in clinical trials. Now that the first peek at the future is available, investigators can focus on developing a wide variety of other innovative approaches to achieve sustained suppression of VEGF in the eye. ■

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