

# Rethinking the Regimen for Retinal Disease Management

Micropulse laser may extend anti-VEGF treatment intervals in several retinal diseases.

BY AHAD MAHOOTCHI, MD

There is no doubt that anti-VEGF drugs have had a significant positive impact on the treatment of multiple retinal conditions. However, given the chronic nature of certain conditions, lifelong injection regimens present concerns with certain patient populations. Some patients may not have sufficient financial means or ability to attend appointments on a consistent basis; others may experience negative side effects from overuse of therapies.

A retrospective review of the ANCHOR and MARINA trials by Rosenfeld and colleagues found that, although 38% of patients in ANCHOR and 30% of patients in MARINA gained at least 15 letters of visual acuity at 24 months, 9% and 10% of patients in the 2 trials, respectively, lost 15 or more lines of visual acuity over the same time period.<sup>1</sup> The loss of visual acuity in both trials was associated with retinal pigment epithelium (RPE) abnormalities that the authors speculated were related to geographic atrophy.

The CATT also found a link between treatment and geographic atrophy.<sup>2</sup> At 2 years, the prevalence of geographic atrophy was higher among patients treated monthly with either ranibizumab (Lucentis, Genentech) or bevacizumab (Avastin, Genentech) compared with those treated on an as-needed schedule.

Development of chorioretinal atrophy has also been found to occur frequently in patients treated with anti-VEGF agents for myopic choroidal neovascularization, affecting visual improvement.<sup>3</sup>

Studies in a mouse model analyzing the role of VEGF in the RPE suggest that VEGF is an important neuroprotective protein that has a functional role in supporting adult subretinal vasculature, including the choriocapillaris.<sup>4</sup> The choriocapillaris, in turn, nurtures cones and photoreceptors and maintains central vision.

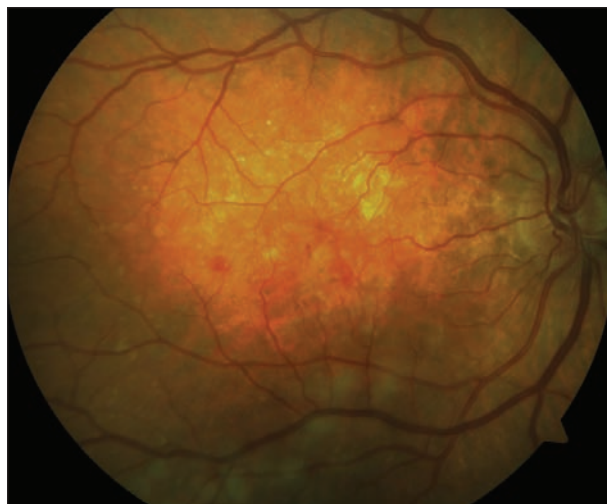


Figure 1. Fundus photograph showing atrophy.

These findings have been followed by recent studies confirming the association of geographic atrophy with sustained visual acuity loss in patients with age-related macular degeneration (AMD) undergoing anti-VEGF therapy.<sup>5</sup>

With my own patients, I observe the same atrophy phenomenon. Atrophy leaves watermarks, or “swiss cheese” holes, in patients’ vision that counteract the visual acuity benefits of anti-VEGF therapy (Figure 1).

Considering these negative side effects from overuse of anti-VEGF therapy along with related cost and convenience issues, it is essential to find an optimal therapeutic regimen. In my practice, I have found the use of micropulse laser therapy with the Iridex IQ 577 laser to be complementary to anti-VEGF injections in patients with AMD and effective for treatment of several other retinal vascular diseases.

## STIMULATING THE RPE AND UPREGULATING CERTAIN ANGIOGENIC INHIBITORS

Micropulse laser is unlike traditional continuous-wave laser photocoagulation aimed at destroying abnormal blood vessels. The technology essentially chops the continuous-wave beam into a train of repetitive short pulses, allowing treated tissue to cool between pulses, therefore reducing thermal buildup. Rather than damaging tissue, micropulse laser induces a stress response that upregulates certain angiogenic inhibitors, such as pigment epithelium derived factor (PEDF), and downregulates inducers of VEGF.<sup>6,7</sup> This beneficial intracellular biologic activity is antiangiogenic and restorative. There may also be other ways it works to stimulate the RPE.

There are no lethal photothermal effects at a 5% duty cycle. The laser clearly works by some nonburning, non-traditional mechanism. No laser lesions are discernible via fluorescein angiography or fundus autofluorescence (FAF).<sup>7</sup> This allows the clinician to treat directly over the fovea without worry.

Multiple investigators have shown 810 nm micropulse laser therapy to be effective in the treatment of diabetic macular edema (DME),<sup>8,9</sup> branch retinal vein occlusion,<sup>10</sup> and central serous chorioretinopathy.<sup>11</sup> It is also worth noting that, in the READ-2 study, when traditional laser was added to ranibizumab for the treatment of DME, patients required fewer injections over 24 months than those receiving pharmacotherapy alone (4.9 vs. 9.3), with similar visual acuity results.<sup>12</sup>

## CASE REPORT

I have found similar results in my own practice. For example, a 71-year-old woman presented with neovascular AMD in her right eye after losing the left eye's vision to wet AMD. She was treated with intraocular bevacizumab every 6 weeks for a number of years and achieved a best visual acuity of 20/40 after 31 injections. However, she was often symptomatic at the end of each 6-week interval, and geographic atrophy was becoming more pronounced on her fundus examinations (Figure 2).

I performed transfoveal micropulse therapy with the Iridex IQ 577 laser. Her cysts slowly resolved and visual acuity improved to 20/25 (Figure 3). Eight months have passed since her last bevacizumab injection, and the patient still does not need another.

It takes time to see a positive effect with micropulse laser therapy. Cells are being stimulated to produce their own antiangiogenic activity, a process that is slower than injecting a drug. However, in my experience, micropulse laser can last much longer, and it eliminates side effects such as the development of geographic atrophy.

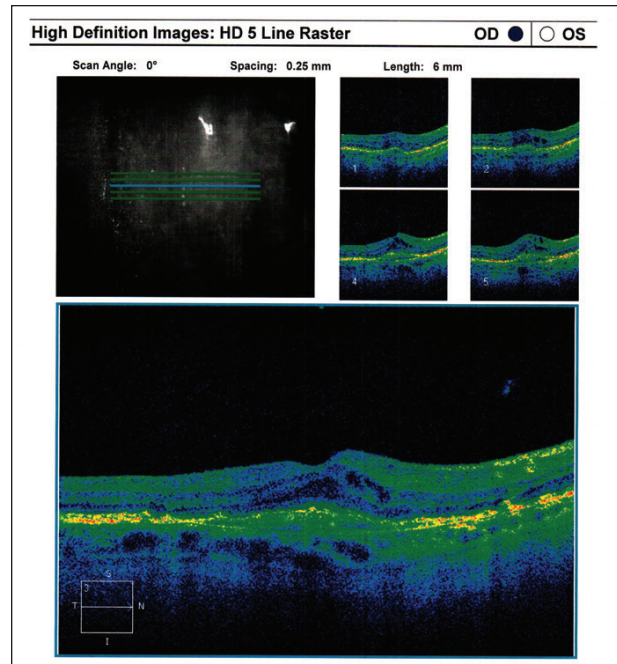


Figure 2. Optical coherence tomography scan of a patient following multiple injections of bevacizumab every 6 weeks.

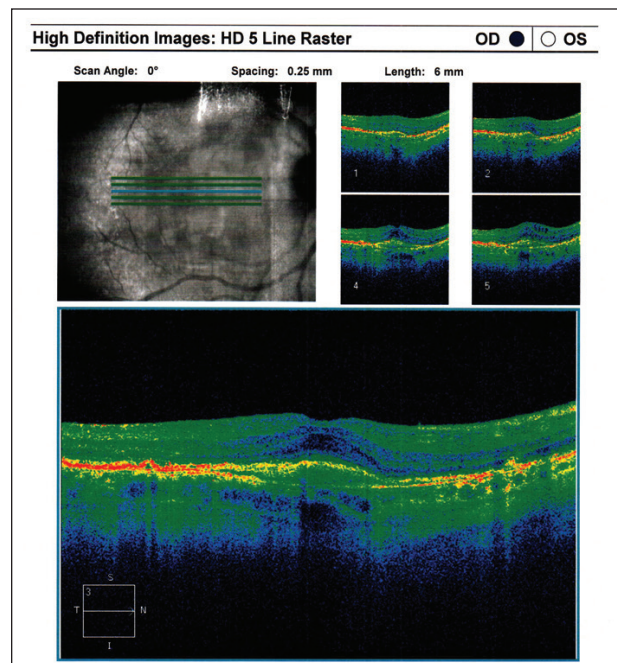


Figure 3. The same patient as in Figure 2 after micropulse therapy through the fovea, showing stabilization and objective improvement.

## INCREASED BENEFITS

With the adoption of micropulse laser I have also seen measurable financial benefit for my practice and for

patients. I was previously spending \$40 000 per month to purchase anti-VEGF injections. Since I have incorporated micropulse, I can meet the clinical needs of my patients with only \$13 000 of drugs per month. This may not matter for the insurance plans of some patients, but from a practice management standpoint, less capital is tied up in inventory and, thus, available for alternative business investments, such as more staff to manage a greater number of patients. Patients are happy because they need fewer office visits and fewer uncomfortable injections.

### CHANGE MONTHLY INJECTION REGIMENS

We are in an era when 2 trends are intersecting: The number of patients with retinal diseases is rising, and expenses related to pharmaceuticals are growing. It seems logical to rethink our treatment regimens to maximize the clinical effect for our patients. Not only are injections costly and inconvenient, reducing the likelihood of compliance, but they also can have serious side effects. Micropulse laser therapy has been found to be an effective adjunctive treatment for several retinal vascular diseases, and anecdotal evidence suggests that the same is true for AMD. This treatment modality merits a larger study to define the best ways to use the therapeutic tools we have in a synergistic fashion. ■

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- Rosenfeld PJ, Shapiro H, Tuormi L, et al. Characteristics of patients losing vision after 2 years of monthly dosing in the phase III ranibizumab clinical trials. *Ophthalmology*. 2011;118(3):523-530.
- Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: 2-year results. *Ophthalmology*. 2012;119(7):1388-1398.
- Oisha A, Yamashiro K, Tsujikawa A, et al. Long-term effect of intravitreal injection of anti-VEGF agent for visual acuity and chorioretinal atrophy progression in myopic choroidal neovascularization. *Graefes Arch Clin Exp Ophthalmol*. 2013;251(1):1-7.
- Kunihara T, Westenskow PD, Bravo S, et al. Targeted deletion of VEGFA in adult mice induces vision loss. *J Clin Invest*. 2012;122(11):4213-4217.
- Ying GS, Kim BJ, Maguire MG, et al. Sustained visual acuity loss in the Comparison of Age-Related Macular Degeneration Treatments Trials. *JAMA Ophthalmol*. 2014;132(8):915-921.
- Ogata N, Tombran-Tink J, Jo N, et al. Upregulation of pigment epithelium-derived factor after laser photocoagulation. *Am J Ophthalmol*. 2001;132:427-429.
- Vujosevic S, Bottega E, Casciano M, et al. Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. *Retina*. 2010;30(6):908-916.
- Lavinsky D, Cardillo JA, Melo LA Jr, et al. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2011;52(7):4314-4323.
- Luttrull JK, Sramek C, Palanker D, et al. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. *Retina*. 2012;32(2):375-386.
- Parodi MB, Spasse S, Iacono P, et al. Subthreshold grid laser treatment of macular edema secondary to branch retinal vein occlusion with micropulse infrared (810 nanometer) diode laser. *Ophthalmology*. 2006;113(12):2237-2242.
- Koss MJ, Begerl J, Koch FH. Subthreshold diode laser micropulse photocoagulation versus intravitreal injections of bevacizumab in the treatment of central serous chorioretinopathy. *Eye (Lond)*. 2012;26(2):307-314.
- Nguyen OD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the macula in diabetes (READ-2) study. *Ophthalmology*. 2010;117(11):2146-2151.