

June 2010, Issue 42

The "Treat and Extend" Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration

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This work is supported by The Macula Foundation, Inc..



While monthly injection of intravitreal anti-vascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration (AMD) have produced visual outcomes superior to prior therapies,^{1,2} the frequency of office visits and injections can place a tremendous burden on patient and the health care system. Unfortunately, the PIER trial,³ which is the only randomized, double-blind, sham-controlled trial investigating a less frequent dosing regimen, yielded inferior visual outcomes compared to outcomes reported after monthly dosing. Patients in the PIER trial were examined and treated

quarterly following an initial series of three monthly injections. The open label, non-randomized PrONTO study also employed three initial monthly injections but was followed by "as needed" dosing based on changes in visual acuity, clinical findings and optical coherence tomography (OCT) evaluation.^{4,5} The PrONTO regimen appeared to achieve visual results similar to monthly dosing with fewer injections, but patients still required monthly visits, examination, and OCT. Furthermore, after the initial mandated series of three injections, this protocol allowed fluid to re-accumulate at the fovea before treatment was repeated, raising concerns regarding incremental long-term vision loss and the possibility of new hemorrhages during periods without VEGF inhibition.^{6,7,8}

The "Treat and Extend" dosing regimen is a tailored maintenance regimen intended to achieve optimal visual results with two additional goals.⁹ Like PIER and PrONTO, it consists of at least three initial monthly injections, but, once stable visual acuity, an absence of macular hemorrhage, and a dry OCT have been achieved, patients continue to receive regular maintenance injections at increasing intervals. Once stability is achieved with monthly dosing, the patient is instructed to return in six weeks. Visual acuity, clinical findings, and OCT changes are recorded again and patients receive an injection regardless of the presence or absence of disease activity. However, the interval to the next visit (and scheduled injection) is based on an observed change in the above parameters. If there are no changes, the interval to the next visit is extended to seven or eight weeks (hence the term "Treat and Extend"). However, if there is evidence of renewed disease activity, the interval for the next scheduled injection and examination is shortened. In our own clinical practice, we rarely extend the interval between injections and examination beyond 8-9 weeks.

One goal of "Treat and Extend" is to reduce the treatment burden by reducing number of patient visits and the number of imaging studies performed by eliminating the need for the monthly visits necessitated by alternative dosing strategies. We recently reported success in achieving this goal in two small cohorts of eyes with newly diagnosed type 1 (occult)¹⁰ and type 3 (retinal angiomatous proliferation)¹¹ neovascularization. In these reports, the eyes with type 3 vessels had a sustained visual improvement of approximately 2 Snellen lines while the eyes with type 1 vessels achieved visual stabilization. The number of office visits and injections was reduced by 25-50% compared to a monthly dosing regimen.

A second goal of the "Treat and Extend" dosing regimen is to reduce the risk of new sight-threatening submacular hemorrhages. We recently demonstrated a statistically significant increase in macular hemorrhages when patients in the PIER trial were switched from a monthly to quarterly dosing regimen.⁶ Unfortunately, large and potentially devastating submacular hemorrhages may occur almost immediately after a high-quality OCT examination showing an absence of fluid.^{7,8} Theoretically, eyes treated with an OCT-guided "as needed" regimen, in which patients may go long intervals without VEGF suppression, could be at a greater risk for sight-threatening submacular hemorrhage compared to eyes receiving more frequent and regular anti-VEGF treatments. In our two retrospective series, we did not observe any sight-threatening macular hemorrhages. Also, unlike the ANCHOR, MARINA and PrONTO studies which are limited to 24 months of follow-up, 17 of our 28 patients completed 36 month follow-up. We are not aware of any other dosing regimen of anti-VEGF therapy that has demonstrated stable or improved VA out to three years.

While initial results of the "Treat and Extend" dosing regimen appear promising, the strategy requires further validation in a larger randomized trial. Clinicians should view the current data regarding different regimens critically when deciding which dosing strategy is best for individual patients.

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Erratum

We apologize that last month's article, *Comparison of Two Doses of Intravitreal Bevacizumab as Primary Treatment for Subfoveal CNV Associated with AMD at 24 Months: The Pan-American Collaborative Retina Study Group* by J. Fernando Arevalo, MD, FACS and Martin A. Serrano, MD was originally scheduled for a later issue but was in error released in May 2010