# Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration

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AGE-RELATED MACULAR DEGENERATION (AMD) IS increasing in incidence and prevalence among the world's population. Inhibition of the vascular component of AMD has been attempted with a variety of approaches, but the development of the pan-vascular endothelial growth factor (VEGF)-A blocker, ranibizumab (Lucentis, Genentech, South San Francisco, California, USA), for the treatment of choroidal neovascularization (CNV) has been a triumph of modern medicine.[1] Ranibizumab is an antibody fragment that binds all active isoforms of VEGF-A, rendering them inactive. It was developed through an exhaustive process that required modifying a murine monoclonal antibody to derive an antibody fragment, and affinity maturing the fragment to restore and even improve VEGF binding. Patients with neovascular AMD treated in phase 3 trials using this medication experienced an improvement in visual acuity. In the MARINA trial, which examined minimally classic or occult with no classic disease, patients receiving 0.5 mg of intravitreal ranibizumab on a fixed monthly schedule had a mean improvement of 7.2 letters, while sham-treated controls lost 10.4 letters over the course of the first year.[2] In the ANCHOR trial, patients receiving 0.5 mg of intravitreal ranibizumab on a fixed monthly schedule had a mean improvement of 11.3 letters, while controls treated with photodynamic therapy that used verteporfin had a mean loss of 9.5 letters over the first year.[3]

Along with the triumph of ranibizumab comes the bill. The drug charge per injection costs patients, or their insurance company, $2,000. The costs estimate increases when the charges for the injection procedure, the ophthalmic examination, and associated tests are added. Economists would add in the costs incurred by the family members taking off work to accompany the patient and lost opportunity costs. The total cost over a year for a single patient is stunning; the cost projections for the United States are staggering. Although economists can convert burdens into the equivalent economic ones, patients and doctors alike often pigeonhole costs. Returning every month for injection and follow-up within two to seven days after the injection, as recommended in the product insert, is a cost, but also is an emotional and psychological burden for the patient, family, and even the doctor. In medicine, risk of treatment is usually associated with the intensity of treatment. Mandated monthly treatment may incur increased risks, particularly if the patient really doesn't really "need" the treatment each month.

In this issue appears an important article by Anne Fung and associates at Bascom Palmer Eye Institute.[4] This study, known as the Prospective Optical Coherence Tomography Imaging of Patients With Neovascular AMD Treated With Intraocular Ranibizumab (Lucentis), or PrONTO, study, led by Phil Rosenfeld, examined a strategy of giving patients ranibizumab on a schedule dictated by a carefully considered list of criteria. At baseline and each visit thereafter, patients had their visual acuity measurements performed with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 2 m when a refraction protocol was used. Patients then were given three injections of ranibizumab at monthly intervals. Five criteria were used to determine whether a patient needed an additional injection at each monthly follow-up examination. Patients were treated again if they had a visual acuity loss of at least 5 letters on the ETDRS chart with optical coherence tomography (OCT) evidence of fluid in the macula, an increase in OCT central retinal thickness of at least 100 μm, new macular hemorrhage, new area of classic CNV seen by fluorescein angiography, or evidence of persistent fluid on OCT at least one month after the previous injection. After one year of follow-up, the patients had a mean visual acuity improvement of 9.3 letters. With the usual caveats about comparing studies, the visual acuity results were similar to those seen in ANCHOR and MARINA. However, patients in the PrONTO study required only 5.6 injections over the first year. The reduced drug costs per patient amount to about half the mean per capita yearly income for older people in the United States.[5] Multiply this dollar amount by the number of patients with CNV that results from AMD and the potential savings are enormous.

If patients can meet the entry criteria of the study and are treated according to the methods used in the study, they would have a reasonable expectation of having similar results. The confidence of this expectation is influenced by a number of factors, including the number of patients in the study. The ANCHOR and MARINA studies both had large numbers of patients, whereas the PrONTO study had 40 patients and no controls. In actuality, PrONTO would

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be difficult to implement for many practices. An ETDRS visual acuity measurement with protocol refraction is a requirement for a rigorous trial and is a time-consuming test administered by a certified visual acuity examiner. This test is not practical for many busy practices. Dropping the need for ETDRS visual acuity measurement as part of the criteria would make the study easier to implement, but at the cost of widened confidence intervals for the expected outcomes.

The reduction in intraocular injections was not associated with marked reduction in visits by the patient to the ophthalmologist's office. Patients still required monthly examinations with monthly OCTs and quarterly fluorescein angiograms to look for classic CNV. An alternative approach would be to look for a method to decrease both the injections and visits in general. In the PIER trial, patients were provided three injections at monthly intervals and then quarterly injections, except the patients were given a final injection at month 11. Even though the patients should have had a fairly good 12-month visual acuity because they had a mandated injection at 11 months, the mean visual acuity dropped by 0.2 letters in the 0.5-mg group. So giving the patients a reduced number of injections—a therapy not based on objective factors of need—appeared to result in a less favorable outcome.[6] In our office, we treat some patients with a technique we call "inject and extend." Patients are provided three monthly injections and then told to return in six weeks. They undergo an ophthalmic examination, including biomicroscopy and OCT. If the patients have no new hemorrhage or signs of exudation such as edema or subretinal fluid they are injected and instructed to return in eight weeks. If they have edema or other signs of exudation, they are given an injection and told to return in four weeks. Patients returning at eight weeks are given the same examination. If there are no signs of disease activity, they are given an injection and told to return in 10 weeks. If they have exudation, they are given an injection and told to return in six weeks. Patients with this strategy would go only a few weeks, at most, of having any sign of exudation. The optimal examination and treatment interval may be quickly established.

It is obvious that monthly treatment is an expensive and burdensome ordeal. The good news is that it works. The PrONTO approach obviates the need for six injections, but still has the cost of monthly examinations. The good news about PrONTO is that it suggests that patients can be treated according to need and have a good outcome. We need to determine and consider what the patient's needs are in aggregate. How can we best address the patient needs, both for good visual outcome and decreased burden to the patient and the patient's family? What are the best criteria to use for retreatment? Is an inject and extend strategy better because it reduces patient visits? These are interesting questions that need to be answered. They could not have been asked without the groundbreaking work of the Bascom Palmer group with the PrONTO study, which to their credit was partly funded by Genentech, the maker of ranibizumab.

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