# Imaging Guides Treatment Decisions in AMD

The role of FA and OCT to guide treatment with anti-VEGF therapy in patients with neovascular AMD.

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## ABSTRACT

**Purpose:** To evaluate the frequency of fluorescein angiographic (FA) leakage and optical coherence tomography (OCT) changes (subretinal fluid, macular edema, pigment epithelial detachment) in patients with neovascular age-related macular degeneration (AMD) receiving antivascular endothelial growth factor (VEGF) therapy (pegaptanib sodium [Macugen, OSI/Eyetech], bevacizumab [Avastin, Genentech], or ranibizumab [Lucentis, Genentech]).

**Methods:** A retrospective interventional study was conducted in patients diagnosed with neovascular AMD and receiving anti-VEGF therapy. We included only visits in which both FA and OCT was obtained and an injection was administered. Images were reviewed to determine evidence of FA leakage and OCT changes.

**Results:** Fifty-three visits were identified to have both FA and OCT images available for interpretation. FA leakage was seen at 50 of 53 visits (94.3 %). OCT changes were seen at 29 of 53 visits (54.7 %). All of the eyes with OCT changes showed evidence of FA leakage, while eyes with no OCT changes showed FA leakage in 21 of 53 injections (39.6%).

**Conclusion:** FA leakage, rather than OCT changes, is more commonly associated with active choroidal neovascularization (CNV) secondary to AMD in patients on anti-VEGF therapy. Ruling out FA leakage may be required when OCT findings are absent prior to skipping injections in the course of treatment of neovascular AMD with anti-VEGF therapy.


## INTRODUCTION

With the introduction of anti-VEGF treatment for neovascular AMD, there has been an unprecedented increase in the clinical use of these medications. There have been a number of studies focusing on ranibizumab treatment in neovascular AMD.[1-5] The MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) studies showed the effectiveness of ranibizumab for treating minimally classic/occult lesions and predominantly classic CNV secondary to AMD respectively,[1,2] while the PIER (Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration) study attempted to demonstrate the effectiveness of treatment every 3 months.[3] The effectiveness of this treatment regimen to stabilize vision was similar to that observed in the MARINA and ANCHOR studies; however, the gained vision maintenance was not observed over the course of the PIER study as in the other two studies.[1-3] This suggests that injections may need to be administered more often than every 3 months in some patients; however, it is unclear what the best protocol is to determine treatment intervals and end points for individual patients. The above-named studies based treatment on time-based guidelines, leaving no role for imaging or exam findings in directing treatment. The PrONTO (Prospective OCT Imaging of Patients with Neovascular AMD Treated with Intraocular

**TABLE. RESULTS**

| | OCT + | OCT - | Total |
|---|---|---|---|
| FA+ | 54.7% (29/53) | 39.6% (21/53) | 94.3% (50/53) |
| FA- | 0.00% (0/53) | 5.67% (3/53) | |
| Total | 54.7% (29/53) | | |

*Positive FA (+) defined as leakage*
*Positive OCT (+) defined as macular edema, subretinal fluid or PED*

Ranibizumab) study helped set guidelines for treatment mainly based on optical coherence tomography (OCT) findings.[4] We have noticed that many patients with neovascular AMD while receiving anti-VEGF therapy showed persistent leakage on fluorescein angiography (FA) without OCT findings (macular edema, subretinal fluid or pigment epithelial detachment [PED]). Our hypothesis is that, as more injections are being administered to patients with neovascular AMD, macular edema, subretinal fluid and PEDs will not be seen on OCT, while those membranes continue to show leakage on FA, indicating persistent active CNV.

## METHODS

A retrospective interventional study was conducted of patients diagnosed with neovascular AMD on anti-VEGF therapy (pegaptanib, bevacizumab or ranibizumab) seen by one physician at the Kresge Eye Institute in Detroit, MI. Institutional review board approval was obtained. We included only visits in which both fluorescein angiography and optical coherence tomography were available for interpretation and an injection was given on that same day. Exclusion criteria included eyes with disciform scars, CNV secondary to causes other than AMD, and patients with co-existing diseases that can lead to macular pathology such as diabetic macula edema. Actual images, not charts, were reviewed to determine evidence of fluorescein leakage, and OCT findings (macular edema, subretinal fluid or PED). The entire macula was examined when evaluating leakage on FA. Leakage falling outside of the 6-mm scanned area on OCT was noted. OCT images were obtained with the Stratus OCT (Carl Zeiss Meditec, Dublin, CA). All scanned images were reviewed for evidence of subretinal fluid, macular edema and PED.

## RESULTS

Fifty-three visits in which injections were given were identified to have both FA and OCT images available for interpretation. Anti-VEGF therapy included seven pegaptanib injections, 29 bevacizumab injections, and 16 ranibizumab injections. FA leakage was seen at 50 of 53 visits (94.3%). No FA leakage was observed outside of the 6-mm OCT scanned area. OCT changes in the form of subretinal fluid, macular edema or PED were seen in 29 of 53 injections (54.7%). Subretinal fluid alone was seen in six of 53 injections (11.3%) while macular edema alone was seen in 11 of 53 injections (20.8%). PED alone was seen in two of 53 injections (3.8%). All of the eyes with OCT changes showed evidence of FA leakage, while eyes with absent OCT changes showed FA leakage in 21 of 53 injections (39.6%) (Table).

## DISCUSSION

The MARINA and ANCHOR studies showed the effectiveness of ranibizumab for treating CNV secondary to neovascular AMD.[1,2] In the MARINA study[1] at one year, 94.6% of patients treated with 500 µg of ranibizumab maintained their vision (losing fewer than 15 ETDRS letters). More important, 33.8% of patients gained vision (gaining 15 ETDRS letters or more). The ANCHOR study[2] demonstrated 96.4% of patients treated with 500 µg of ranibizumab maintained their visual acuity and 40% of these patients gained vision. Although these two studies demonstrated the effectiveness of ranibizumab injected monthly on patients with all types of neovascular AMD, the PIER study[3] attempted to demonstrate the effectiveness of treatment with intravitreal ranibizumab every 3 months after 3 monthly injections at the start of the study. At 1 year, 90% of these patients maintained their vision. This number is comparable to the MARINA and ANCHOR studies; however, when it is considered that only 13% of patients gained vision, it becomes evident that this dosing schedule may not be as effective in some patients.[3] Clearly these studies are different in design and cannot be statistically compared, but the trend suggests that in some patients it is necessary to treat more often than every 3 months.

In all of these studies, patients received monthly injections or injections every 3 months for a 2 period without regard to either clinical findings or retinal imaging.[1-3] These studies are extremely valuable demonstrating the clinical response of neovascular AMD to ranibizumab; however, the rigid injection schedule used in theses studies leaves little room for clinicians to choose to skip injections based on presentation.

The PrONTO study[4] helped to define an algorithm for treatment using imaging and clinical findings. The study

It appears that FA is more sensitive in the presence of active CNV. This may suggest that FA should be used at each visit when a decision is being made to skip an injection.

used three monthly injections to start the trial. Following this monthly OCT imaging was used, as well as FA studies every 3 months. Patients were treated with ranibizumab injections if OCT thickness increased by 100 µm, if visual acuity decreased by 5 ETDRS letters with associated OCT changes, or if there was new-onset CNV or subretinal hemorrhage. Using OCT to direct treatment, 95% of patients lost fewer than 15 letters. These numbers are similar to the ANCHOR, MARINA and PIER studies, however, when comparing visual gain the study still lags behind ANCHOR and MARINA. At the conclusion of the study, PrONTO showed an average gain of 9.3 letters compared to 11.3 and 14.4 letters gained in ANCHOR and MARINA respectively.[1-4]

Again, it would be inappropriate to compare these studies' outcomes, but general trends remain; with monthly injections vision is better maintained at the expense of possibly overtreating the patient, and using OCT changes as a guide for treatment seems to have more favorable outcomes than injections every 3 months. The question ophthalmologists must answer is why OCT-guided treatment does not demonstrate similar results as the monthly injection protocols. If all active disease is detected with monthly OCT, the treatment outcomes should parallel injecting patients every month.

Our study demonstrated that all eyes with OCT changes showed evidence of FA leakage; conversely, 39.6% of eyes absent OCT changes showed FA leakage. The absence of OCT change in the face of leakage may be secondary to a relatively healthy RPE pumping fluid out of the retina and maintaining retinal integrity in the face of mildly active disease. Whatever the reason, it seems there are situations in which active disease is found on FA, but the lesion is subclinical on OCT. If these patients are determined to be quiet based on OCT guidelines and an injection is skipped, they may return at the next visit with edema and decreased visual acuity that may have been avoided if FA was used to identify leakage. CNV still present but not leaking enough to cause retinal thickening or subretinal fluid measurable on OCT may form the basis for recurrent leakage and the failure to gain visual acuity improvement noted in the PrONTO study compared with the ANCHOR and MARINA studies.[1,2,4]

Based on this small retrospective study, it appears that FA is more sensitive in these cases to the presence of active CNV. This may suggest that FA should be used at each visit when a decision is being made to skip an injection, despite absent OCT findings.

This study has the limitations of being retrospective and having a small sample size. The correlation between FA leakage and OCT findings in our study shows much higher incidence of FA leakage compared with visible changes on OCT in patients with neovascular AMD on anti-VEGF therapy. This wide gap between those two tests may be explained by our practice of ordering more FAs with OCTs at visits when a decision was made whether to skip an injection.

We examined OCT images from the Stratus OCT. Small areas of subretinal fibrosis or macular edema between the six radial scans may have been missed, especially with less active disease. Furthermore, the availability of spectral OCT may make that tool more sensitive in detecting minimal changes on OCT corresponding to persistent FA leakage, not previously detected on the Stratus OCT.

A prospective randomized study in which continued anti-VEGF treatment is based on either OCT or FA would help provide useful clinical guidelines for the best imaging tool to assist in treatment of CNV associated with AMD. ■

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