REVIEW of OPHTHALMOLOGY
Clinical advice you can trust

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When Anti-VEGF Treatment Fails

Retina specialists are charting new territory and learning how to spot and react to failed anti-VEGF therapy.

Anti-VEGF therapy has become the mainstay for managing patients with wet macular degeneration. While the response rate in published studies ranges from 70 to 95 percent depending on the agent used and the treatment paradigm employed, it is clearly not 100 percent, and some patients do fail treatment. It is these treatment failures that usually represent the most challenging cases. Here, I review the limited data available that relates to the management of such treatment failures and present our evolving approach for these uncommon and complicated cases.

Recognizing Treatment Failures

There is no universally agreed upon definition of treatment failure. Some clinicians identify a treatment failure when multiple anti-VEGF treatments have been applied and fluid or leakage persists on optical coherence tomography or fluorescein angiography, respectively. Others deem treatment a failure when vision loss continues despite a course of treatment. There is also the concept of "treatment disappointments," for example, when continuous monthly injections are required to keep the macula dry or

where treatment produces a decrease in edema but no improvement in vision.

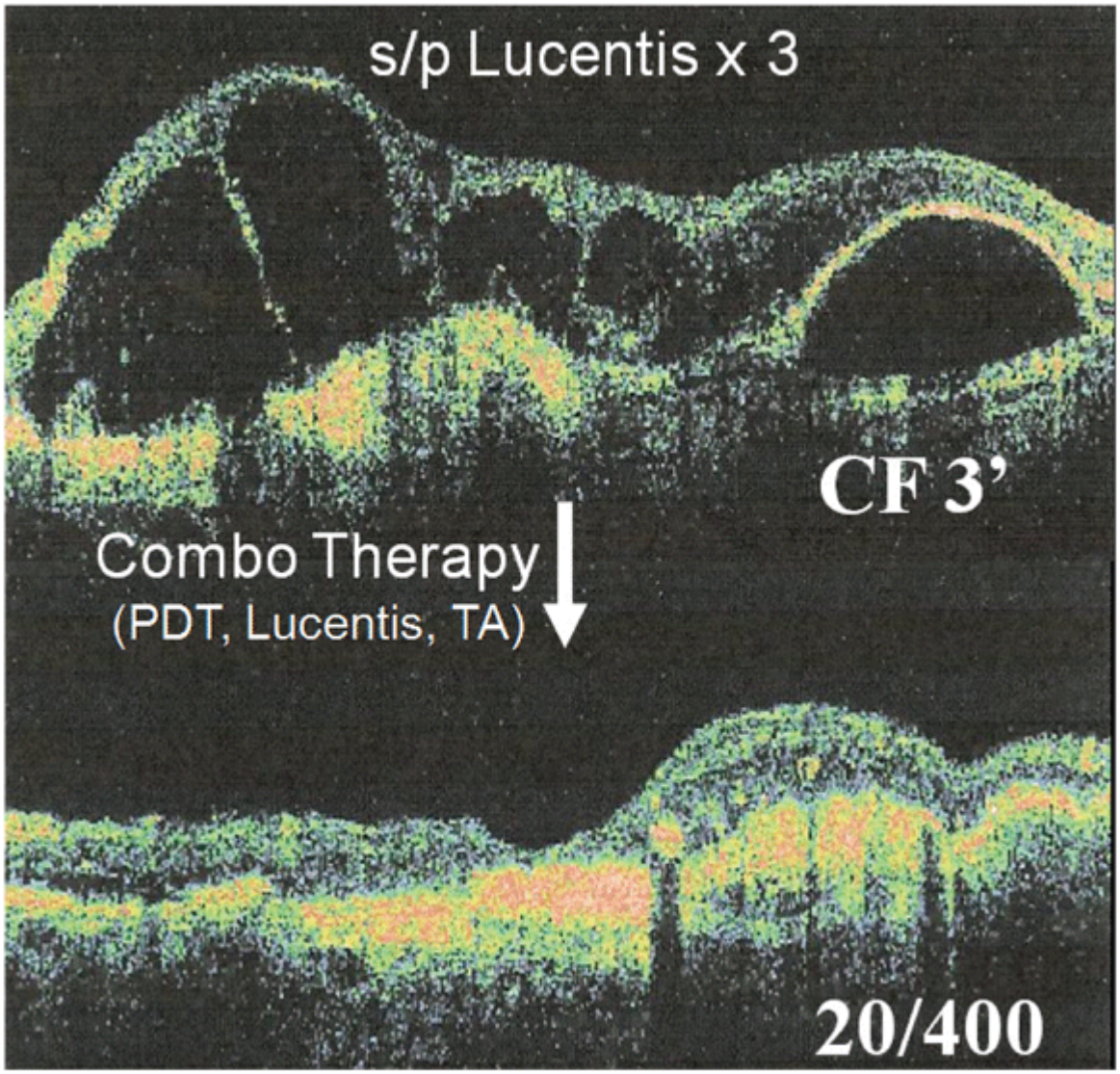


Figure 1. Rescue therapy of advanced case of wet age-related macular degeneration with triple combination therapy after failed treatment with Lucentis.

For practical purposes, I define treatment failures as those patients who no longer respond with an improvement in macular edema on OCT or a reduction of leakage on fluorescein angiography following treatment with an anti-VEGF agent. Figure 1 illustrates a treatment failure of Lucentis in an advanced case of wet age-related macular degeneration with subsequent response to combination therapy utilizing Lucentis, Visudyne and intravitreal injection of unpreserved triamcinolone acetate.

Macugen Treatment Failures

The approach to treatment failures clearly relates to the agent associated with the treatment failure. In the case of pegaptanib (Macugen), for example, the approach has been straightforward: switch to an alternative anti-VEGF agent with a response rate clearly greater than that of pegaptanib. Pegaptanib was the first approved anti-VEGF treatment for the management of wet

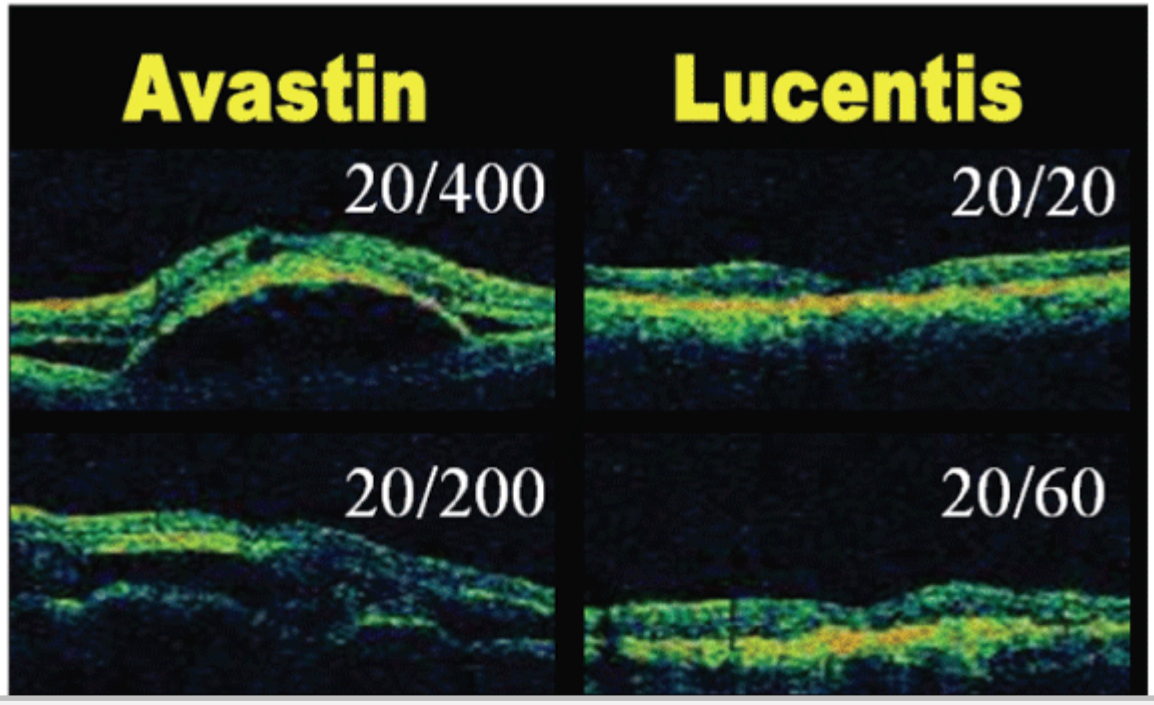
most frequently associated with neovascularization—the VEGF 165 isoform. While data supports a treatment effect for Macugen with a maximal response rate of about 70 percent, there were significant treatment failures with this agent, as well as "treatment disappointments" in a substantial proportion of "responders" who continued to lose vision over time.

In contrast, the second approved anti-VEGF agent, Lucentis, exhibited a response rate of 95 percent. Thus, most retina specialists have utilized the more potent anti-VEGF agent Lucentis, and its off-label cousin, Avastin, for the management of Macugen treatment failures. As a result, Macugen is now rarely used as a sole treatment for wet AMD. In a limited study that was prematurely halted, the addition of PDT with intravitreal Macugen did not appear to improve response rates and PDT alone is not routinely used for rescue therapy.

Lucentis, Avastin Treatment Failures

Lucentis and Avastin are anti-VEGF agents derived from monoclonal antibodies that can bind all subtypes of the VEGF molecule. Lack of selectivity for VEGF has not been associated with feared complications such as detectable loss of normal retinal capillaries, and the much higher response compared to Macugen suggests that more VEGF isoforms may be involved in pathologic choroidal neovascularization. With a response rate of 95 percent for Lucentis and an empirically comparable rate for Avastin, failures are uncommon. Failures are difficult to predict but one study found that the efficacy of anti-VEGF therapy appears to depend on the initial lesion size and initial reading ability. With a bigger choroidal neovascular size and a lower reading ability, the chance of responding appears to be reduced.

Treatment protocol may also affect response rates and efficacy. The initial Lucentis studies—Marina and ANCHOR—utilized a "fixed-interval treatment protocol" whereby patients received monthly injections for one year. Physicians began to deviate from this protocol for a variety of reasons including empirical data for VEGF upregulation, higher theoretical risk of endophthalmitis and intolerance of scheduled monthly injections by patients. Many adopted the "treat-and-observe" approach, in which a few scheduled injections are given and then the patient is observed, with retreatment performed if "significant" edema or vision loss develops at subsequent visits. While a reduced frequency of injections could be achieved, some treatment failures may be related to this treat-and-observe protocol.



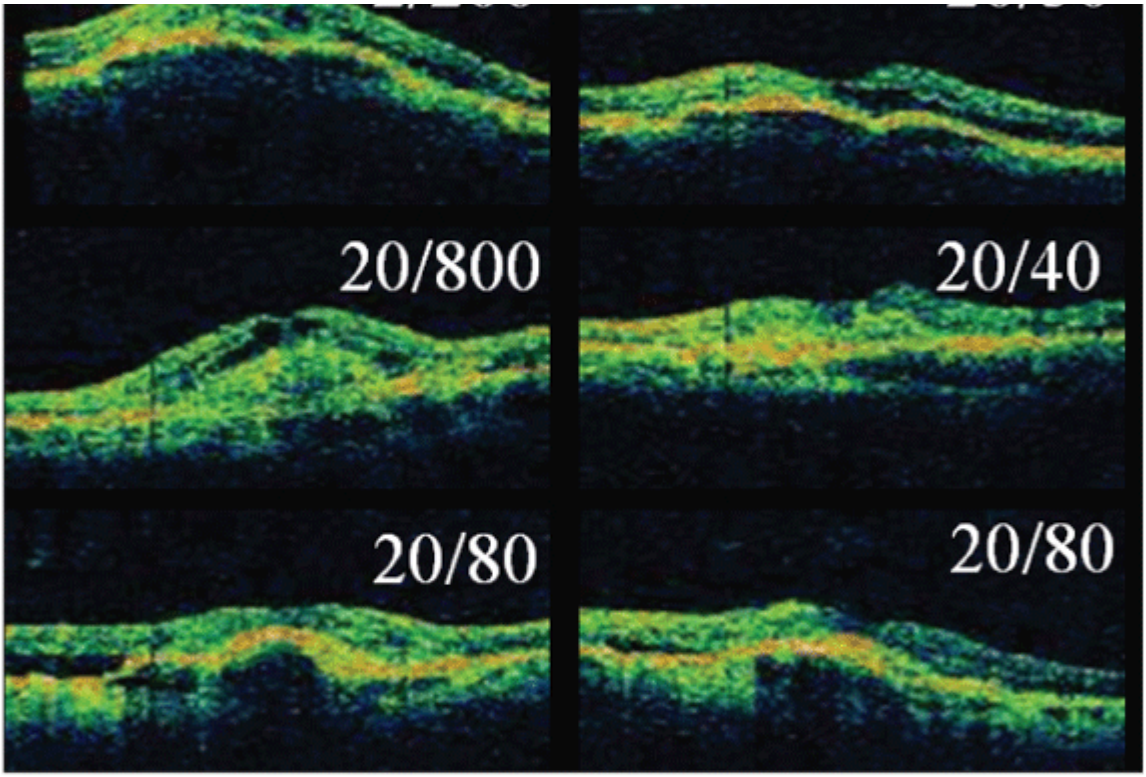


Figure 2. Rescue therapy of Avastin treatment failures with Lucentis. Panel on left shows optical coherence tomography measured after a series of Avastin injections (left) and the panel on the right shows the improvement following a series of Lucentis injections (right).

In the PrONTO study, a treat-and-observe protocol was utilized in which patients received three initial monthly injections of Lucentis and were retreated only when: a) they lost more than five letters of vision and had any fluid on OCT; b) they developed new retinal hemorrhage or classic choroidal neovascularization; or c) there was an increase of >100 µm of edema documented on the OCT.

While the visual acuity results achieved at one year in the PrONTO study were comparable to the results achieved with monthly dosing in the Phase III MARINA and ANCHOR trials, the percentage of patients with an overall decrease in vision was higher, raising concerns about the treat-and-observe approach utilized in the study.

every four weeks to every six weeks and so on until reinjections are scheduled three months apart. If edema recurs between visits the protocol is reinitiated. This protocol may reduce the rate of treatment failures for both Avastin and Lucentis.

When the SAILOR study allowed treatment of patients with wet AMD after they had failed other therapies, we gained experience with the use of Lucentis as rescue therapy. In my practice, the majority of patients were receiving Avastin off-label, since published data suggested this was the most effective therapy for treatment of non-study patients with wet AMD. Of the 13 Avastin treatment failures I treated with Lucentis, 10 responded with a reduction in edema and/or improvement in best corrected visual acuity.

Examples of six best responses on OCT (*greatest reductions in edema*) are shown in Figure 2. All 13 patients had occult choroidal neovascularization with a fibrovascular pigment epithelial detachment. One patient developed a retinal pigment epithelial tear outside of the fovea but still recovered 20/25 vision for nearly one year until he recurred and was stabilized with a triple-therapy regimen (*Avastin/Visudyne/Dexamethasone, see below*).

Combination Therapies

Combination therapy is most commonly used as rescue therapy for patients failing anti-VEGF treatment. The treatment protocols are based on the idea that a multi-pronged approach may be more effective than any single approach since multiple factors contribute to wet AMD including: 1) abnormal VEGF production; 2) inflammatory mediators; and 3) increased vascular permeability of choroidal neovascular membranes (*See Figure 3*). In theory, by attacking each of these three areas—VEGF with anti-VEGF agents, inflammation with corticosteroids, and vascular permeability with photodynamic therapy—we have a better chance of arresting the pathologic process altogether, if not at least for a longer period of time.

The published data support the theory and, in general, combination therapy appears to provide a comparable visual result with a longer duration of effect when compared to anti-VEGF therapy alone.

Combination therapy is also effective for managing most anti-VEGF treatment failures. A variety of combination therapies have been utilized for anti-VEGF treatment failures and in some cases as primary therapy. Most "double therapies" combine an anti-VEGF agent with Visudyne, and there is data supporting efficacy for this approach. Most investigators are utilizing a triple-

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