Use of Low-Voltage X-Ray Adjunctive to Anti-VEGF Therapy in the Treatment of Wet AMD

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Intravitreal injection of an anti-VEGF agent is the standard of care for the treatment of neovascular age-related macular degeneration (AMD). Patients can gain and maintain favorable vision outcomes when anti-VEGF therapy is administered with fixed-interval dosing.[1-4] However, according to the 2014 American Society of Retina Specialists Practice and Trends Survey, more than 90% of physicians globally use as-needed (PRN) or treat-and-extend (TAE) treatment regimens. Several studies have shown inferior results over 2 years with PRN compared with fixed regimens, and there is limited evidence for the efficacy of TAE strategies.[5-8]

Retrospective analyses have shown that average real-world outcomes with anti-VEGF agents are substantially worse than those achieved in clinical trials, with patients experiencing regression of visual gains within 1 to 3 years.[9,10] Part of the reason for this may be the inability of patients and/or their physicians to maintain monthly or extended follow-up schedules. In other scenarios, patients may have an inadequate response to anti-VEGF injections, suggesting the need for an anti-VEGF agent with a higher binding affinity to maintain a fluid-free retina.[11]

VEGF is an angiogenic mitogen specific for vascular endothelial cells that induce angiogenesis (ie, endothelial cell proliferation) and increased vascular permeability. Anti-VEGF agents decrease the vascular permeability of choroidal neovascular (CNV) lesions by binding to VEGF, thus preventing the vision loss caused by retinal edema. However, the size of the CNV lesion may not change—and the vessels may become permeable—if the eye produces more VEGF than can be inhibited by the anti-VEGF agent.[12] Patients with this condition may be termed *lowresponders* or *nonresponders*. Tachyphylaxis has also been reported as a cause of anti-VEGF nonresponse.[13-15] In clinical practice, many patients experience suboptimal visual outcomes despite pharmacologic intervention with anti-VEGF therapy.

LOW-VOLTAGE X-RAY FOR WET AMD: MECHANISMS AND EVIDENCE

Ionizing radiation (IR) has been proposed as an adjunct to anti-VEGF therapy in the long-term management of patients with wet AMD, similar to the combination approach used in oncology for angiogenic tumors. IR disrupts cell mitosis through direct or indirect damage to cellular DNA, thus blunting the formation of new blood vessels. It acts preferentially on cells with rapid cell division cycles (ie, weeks or months), including vascular endothelial cells associated with CNV lesions. Mature cells and cells that are mitotically inactive engage intracellular mechanisms to repair DNA damage and remain viable.

It has been shown in vitro and in vivo that IR greatly enhances the antiangiogenic effects of VEGF suppression, enhancing apoptosis and reducing endothelial cell migration.[16] Stereotactic delivery of microcollimated 100 kV

At a Glance

- Stereotactic radiotherapy may be beneficial for patients who are incomplete responders or non responders to anti-VEGF monotherapy.
- Using multiple approaches at the same time can offer benefits not achievable with monotherapy in the treatment of wet age-related macular degeneration.

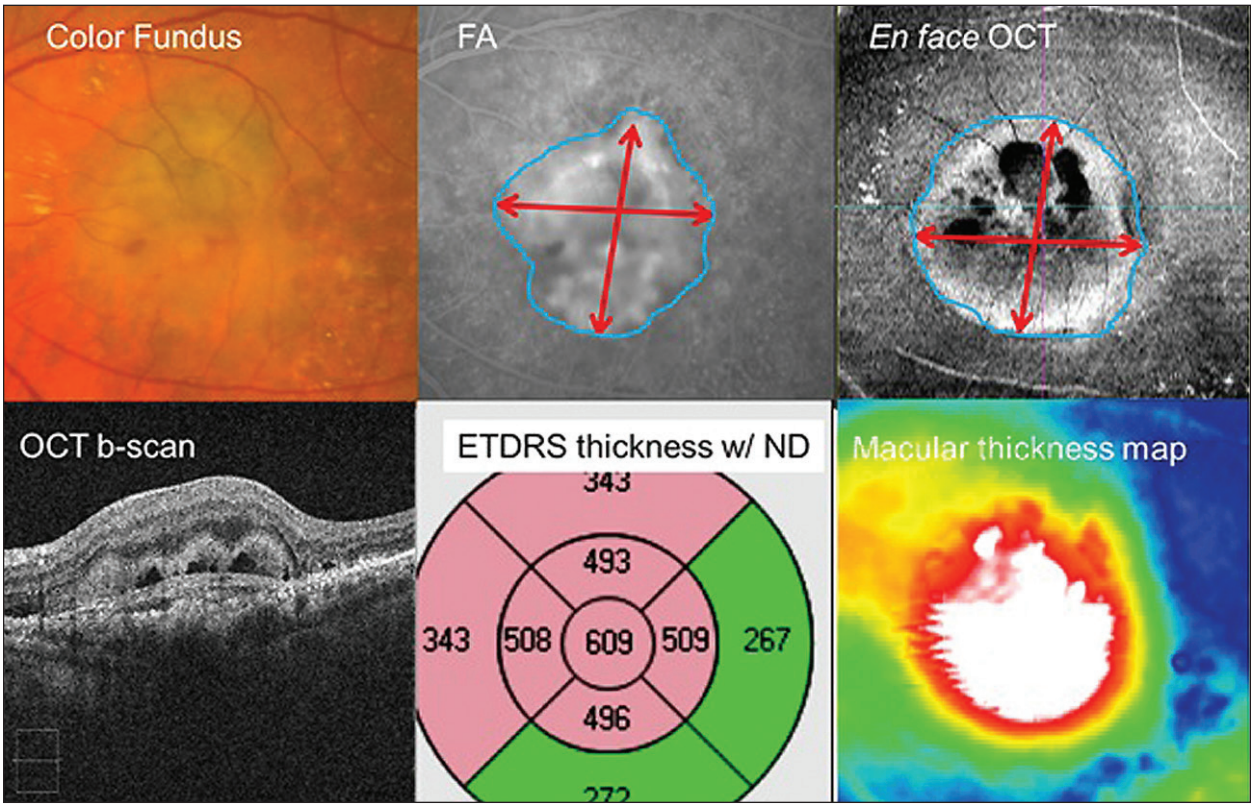


Figure 1. When selecting patients for x-ray SRT, measure the lesion greatest linear dimension using FA (top middle) or en face OCT images (top right). When using OCT B-scans, cycle through consecutive cross-sectional images to find the image depicting the longest lesion length (bottom left). The significance and amount of macular fluid can be quantified using ETDRS sector average thickness with normative data color coding (bottom middle) or macular thickness maps (bottom right).

x-ray irradiation to the retina using the robotically controlled IRay system (Oraya Therapeutics) has been shown to maintain visual acuity gains while reducing the number of injections needed in patients with wet AMD with chronic or recurring disease activity.[17]

The INTREPID study of stereotactic radiotherapy (SRT) was a randomized, double blind, sham-controlled study among patients with wet AMD of the effect of SRT plus PRN anti-VEGF agent or sham SRT plus PRN anti-VEGF agent. The primary endpoint was mean number of anti-VEGF injections at 1 year. The study design and results have been previously reported.[17-19] The study recruited patients with at least three anti-VEGF injections in the previous year who had the need for an additional injection due to continued or recurrent exudative disease activity as determined with optical coherence tomography (OCT) or fluorescein angiography (FA). CNV lesion size was limited to 6 mm in greatest linear dimension. On average, patients entered the study 15 months after diagnosis with wet AMD and had received about 6 injections prior to inclusion.

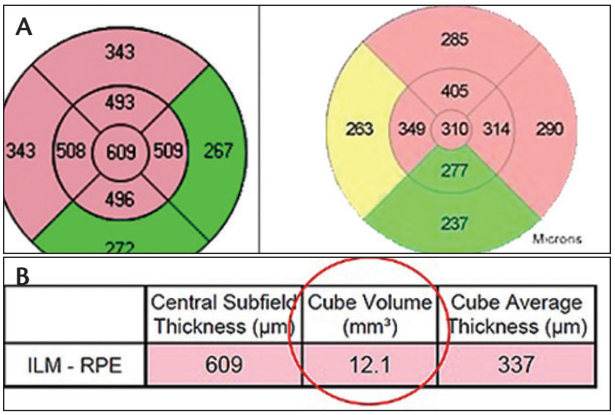
The study met its primary endpoint; patients receiving SRT required 33% fewer injections at 1 year (P = .001) compared with patients receiving sham radiation, while maintaining equivalent vision. At 1 year, 91% of patients in each of the SRT and sham SRT arms lost fewer than 15 letters of visual acuity.

In a post hoc analysis of the influence of baseline characteristics, the greatest benefit was seen in eyes in which the CNV lesion was 4 mm or less in greatest linear dimension and which also experienced significant exudative activity (defined as macular volume > 95% of normal on OCT). In eyes with both of these characteristics, there was a 55% reduction in number of injections (P = .0002) and a greater letter gain of visual acuity compared with sham (P = .028).[19] In relation to the first of these two characteristics, it is notable that the x-ray beam spot size used in the study was 4 mm in diameter.

The treatment benefits persisted through year 2, with significant 25% and 45% reductions in the number of injections in the full cohort and the best-responder group, respectively.

TRANSLATION INTO CLINICAL PRACTICE

SRT using the IRay system has been available for integration into routine care since early 2013 in the United



	Central Subfield Thickness (µm)	Cube Volume (mm³)	Cube Average Thickness (µm)
ILM - RPE	609	12.1	337

Figure 2. OCT can be used to quantify macular thickness within ETDRS sectors and color each sector based on normative data. In these maps, normal is green, and abnormally thick is pale yellow (95th percentile) or pink (99th percentile) (A). Because the IRay system targets a 4.0 mm spot centered on the fovea, look for central involvement. Macular volume may also be quantified with normative data (B).

Kingdom, Germany, and Switzerland. (The device is investigational in the United States.) The first systems were predominantly used in university or public hospital eye clinics, but also a few private eye hospitals. The IRay system uses low-voltage x-ray and integrated shielding to limit radiation scatter and obviate the need for shielding as part of the treatment in almost all installations. The IRay system is easy to integrate into routine clinical practice; however, use of the system requires training in radiotherapy and medical physics (or staff familiar with these) both to assure proper maintenance of the device and to provide the proper patient education necessary for informed consent.

One challenge of integrating the IRay into practice is to extrapolate data from the INTREPID trial to help determine which patients to treat and when.

At a recent manufacturer-sponsored symposium, early adopters of this technology shared how they are approaching the question of which patients to treat.[20] The speakers all said they typically select patients for therapy who meet the profile of best responders from INTREPID, that is, with lesion size less than or equal to 4.0 mm and significant, persistent edema as seen on OCT. The absence of fibrosis was also predictive of better clinical outcomes in INTREPID.[19] However, most patients with chronic CNV have some degree of fibrosis, so these early adopters noted that they generally select patients for therapy with minimal central fibrosis and scarring.

The INTREPID results indicated that neither time since diagnosis nor number of previous injections was predictive of outcomes, so the aforementioned anatomic parameters appear to be the best indicators of potential benefit. CNV

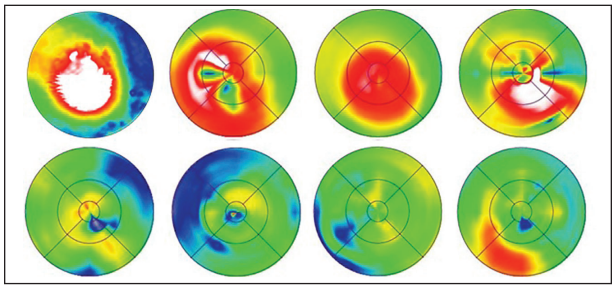


Figure 3. Macular thickness maps offer a quick way to screen patients. The top row presents patients with significant macular fluid centered on the fovea; thus, these are potential candidates for SRT. The bottom row includes images of maculas with lesser degrees of edema or with edema located predominantly outside of the central macula; thus, these eyes are likely not good candidates for SRT.

lesion size can be measured on FA images or by using OCT B-scans or en face images (Figure 1). Abnormal macular volume or thickness can be measured quantitatively using OCT. OCT manufacturers provide various analytics (eg, color coding) to indicate whether a measurement is abnormal (Figure 2). When macular thickness is used to identify lesions that are likely to benefit from IRay, use of central subfield thickness alone is not recommended; rather, the criterion should be presence of abnormal thickness in a majority of ETDRS sectors with central involvement. Qualitatively, OCT macular thickness maps may be helpful for the initial screening of patients (Figure 3).

The question of when to use SRT in eyes with wet AMD was not fully answered by INTREPID. In my opinion, SRT may be helpful in three circumstances:

- In patients who are incomplete responders or nonresponders to anti-VEGF monotherapy. Incomplete response or nonresponse can be defined as no improvement or regression in visual acuity or morphology. Currently there is no clear consensus on the number of injections administered before a patient can be considered not sufficiently or unresponsive to therapy: it has been identified after as few as three monthly injections.[21,22] In this circumstance, the adjunctive use of SRT would be intended to bring the disease under control, thus permitting anti-VEGF therapy to maintain a dry macula.
- In patients whose AMD may be controllable with anti-VEGF, but who require more frequent injections than can be administered practically. The goal in this situation would be to reduce treatment burden.
- In patients at initial diagnosis, during a disease recurrence after extended quiescence, or who are switching anti-VEGF agents, incorporating SRT during the anti-VEGF loading phase may help reduce

the rate of incomplete response or nonresponse and prolong visual acuity gains that have been achieved with fewer injections. It may be optimal to administer SRT with the first loading dose so that the subsequent two injections can help control AMD disease activity while the radiotherapy takes effect (usually 1-3 months).

SUMMARY

Anti-VEGF monotherapy has dramatically improved the potential outcomes for patients with wet AMD. However, results in the clinic may not resemble clinical trial results because of the inability of patients to maintain long-term and frequent follow-ups, or because the patient has incomplete or nonresponse to anti-VEGF therapy or develops tachyphylaxis. As is often the case in medicine, using multiple approaches simultaneously can offer benefits not achievable with monotherapy. Adjunctive use of stereotactic low voltage x-ray therapy has been shown to be effective in controlling wet AMD. Challenges still remain with this technology, however, specifically with regard to ideal patient selection and how best to integrate SRT into clinical practice. ■

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