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The Role of Optical Coherence Tomography in Anti–Vascular Endothelial Growth Factor Therapies

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Anti–Vascular Endothelial Growth Factor Therapies

Vascular endothelial growth factor (VEGF) has emerged as a key mediator of angiogenesis and macular edema in ocular diseases such as neovascular macular degeneration, vein occlusions, and diabetic retinopathy.[1,2] Therapies to neutralize VEGFs action in ocular diseases have been used to successfully combat VEGFs pathogenic role in the eye.

Ophthalmology entered a new era of treatment for neovascular and exudative retinal diseases in December 2004 with the Food and Drug Administration (FDA) approval of pegaptanib (Macugen OSI/Eyetech Inc., Melville, NY) for neovascular age-related macular degeneration (AMD).[3] Pegaptanib, an RNA aptamer that neutralizes VEGF isoforms of at least 165 amino acids, is administered as an intravitreal injection and shown to slow vision loss in neovascular AMD patients. Preliminary work has also been completed on the efficacy of pegaptanib therapy in diabetic macular edema.[4–6]

Another approach to anti-VEGF therapy is ranibizumab (Lucentis, Genentech Inc., South San Francisco, CA), a recombinant humanized antigen-binding antibody fragment that neutralizes all biologically active forms of VEGF, both the isoforms and the proteolytic products. Preclinical trials of ranibizumab were initiated in 2001, and early impressions of the molecule were favorable. The FDA approved ranibizumab for treatment of neovascular AMD in June 2006, and it became the first FDA-approved AMD therapy to maintain or improve vision in ≥90% patients with the potential to improve vision ≥15 letters in approximately one third of patients over 2 years.[7,8]

During the phase III clinical trials of ranibizumab, the clinical benefit of pan-VEGF blockade for neovascular AMD became increasingly clear. A trial was initiated in early 2004 to evaluate the off-label use of an intravenous systemic therapy for patients with bilateral advanced neovascular AMD using a full-length pan-VEGF antibody known as bevacizumab (Avastin, Genentech, Inc).[9,10] Enthusiasm for intravenous bevacizumab as a treatment for AMD was tempered in August 2004 when a warning letter described an increased risk of thromboembolic events in cancer patients undergoing chronic therapy every 2 weeks. Although no thromboembolic events were observed in 18 patients given two or three infusions of bevacizumab over 6 months, the theoretical safety concern limited the off-label systemic use of Avastin.

In May 2005, the intravitreal off-label use of bevacizumab was initiated. Injections of bevacizumab were administered safely with visual acuity benefits for neovascular AMD and macular edema secondary to central retinal vein occlusion.[11,12] Since the use of intravitreal bevacizumab injections was introduced in mid-2005, many additional papers have been published describing the lack of in vitro and in vivo toxicity with intravitreal bevacizumab,[13–16] as well as the clinical safety and efficacy of intravitreal bevacizumab in several ocular diseases,[17–28] and its safety as assessed by an on-line safety survey using the World Wide Web.[29]

Pegaptanib, ranibizumab, and bevacizumab are the three anti-VEGF therapies now available for the treatment of neovascular and exudative diseases of the retina. Optical coherence tomography (OCT) technology matured in parallel during these anti-VEGF therapies and has proven to be uniquely well suited for determining the response to treatment and the need for re-treatment with anti-VEGF therapy. Optical coherence tomography also permits direct visualization and quantification of retinal edema, as well as visualization of other structural pathologic alterations that may or may not be apparent by other imaging techniques such as fluorescein angiography (FA) or indocyanine green (ICG) angiography.

Optical Coherence Tomography in Antiangiogenic Therapy for Wet Age-Related Macular Degeneration

In 1996, Hee et al.[30] published the first paper describing the use of OCT in AMD, stating that OCT was "useful in quantitatively evaluating subretinal and intraretinal fluid, assessing

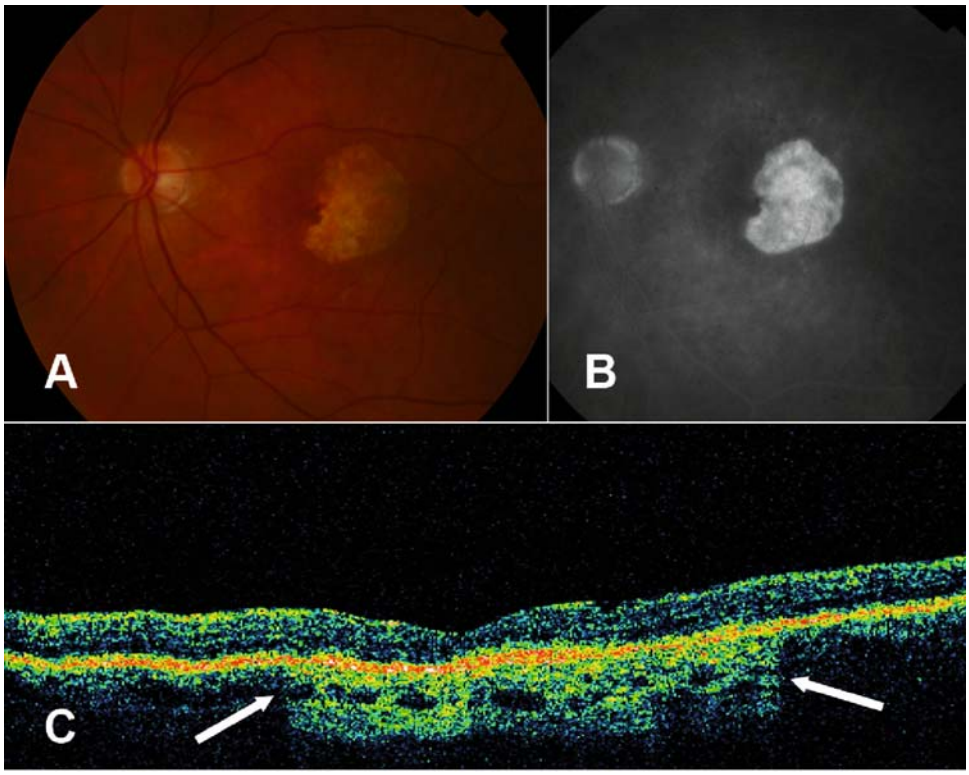


FIG. 15.1. Geographic atrophy on color photograph (A), as a window defect in late-phase fluorescein angiography (B), and on optical coherence tomography (OCT) (C). Central area of OCT shows increased transmission defect (arrows) where OCT scanning beam has penetrated the atrophic retinal pigment epithelium (RPE) to reveal a choroidal shadowing pattern.

possible subfoveal involvement of neovascularization, and in monitoring CNV before and after laser photocoagulation" and that "OCT may have potential in accurately defining the boundaries in a subset of angiographically occult CNV." Since then, OCT imaging for the retina has matured through multiple software versions and has entered the mainstream of AMD management, including photodynamic therapy (PDT) and anti-VEGF treatments.[31–35]

Optical coherence tomography has gained utility in both nonexudative and exudative AMD. In nonexudative AMD, OCT can identify diffuse retinal atrophy, or geographic atrophy of the retinal pigment epithelium (RPE) by a pattern of increased choroidal reflectivity (Fig. 15.1).[36] In neovascular AMD, OCT plays a more important role and includes both diagnosis and management of the disease. A pilot study of macular OCT as a screening tool for exudative AMD concluded that OCT was very sensitive and acceptably specific for this purpose.[37] Optical coherence tomography data are also increasingly used as main outcome measures of clinical results in studies of therapies for exudative AMD.[9,10,17,19,38]

This chapter further discusses the OCT characteristics of neovascular AMD including a quantitatively thickened central retinal thickness (CRT), and qualitative findings including the cystic appearance of intraretinal fluid, subretinal fluid, retinal pigment epithelial detachments (PEDs), and choroidal neovascularization.[10,39–41]

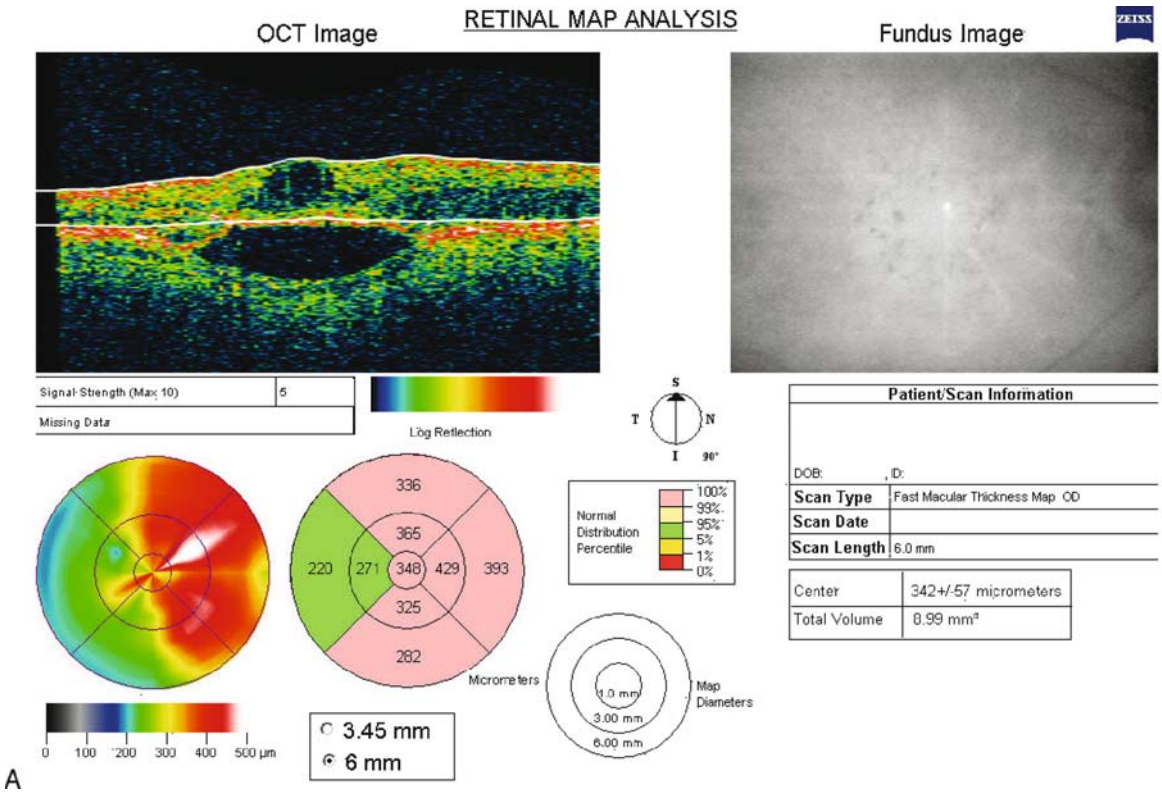
Optical Coherence Tomography Interpretation

Optical coherence tomography evaluation of the macula provides both qualitative and quantitative information.

Fast Macular Maps and Central Retinal Thickness

Central retinal thickness (CRT) measurements are calculated from a fast macular map scan. The OCT scan setting captures six diagonal lines at 30-degree intervals centered on the fovea (like cuts in a pie). To increase the reliability of the thickness data by minimizing patient movement between scans, these six fast lower-resolution (128 A-scans) scans are taken in rapid succession. Ideally, the lines overlap in the fovea to provide an accurate central 1-mm retinal thickness measurement (Fig. 15.2A, black and white image).

The retinal thickness is calculated by measuring the distance between the inner and outer retinal boundaries. The Stratus OCT-3 has an internal algorithm that determines the CRT by tracing the boundaries of the inner retina (vitreous/retinal interface) and the outer retina (the RPE-Bruch's/photoreceptor junction) and calculating the distance in micrometers between these two boundaries (Fig. 15.2A, color image).



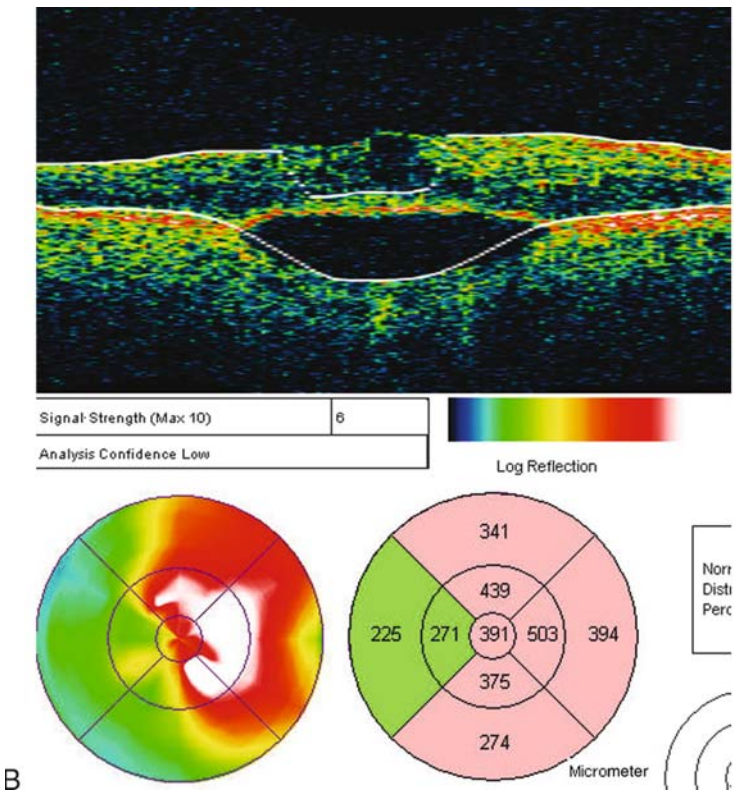


FIG. 15.2. (A) Baseline fast macular thickness map. Top left: The single low-resolution line scan shows the white line tracing the Stratus OCT's algorithm for tracing the internal and external boundaries of the retina. Bottom left: The first circle provides topographic representation of retinal thickening in the central 6-mm macula. The second circle presents macular thickness data: central retinal thickness (CRT) is 348 µm, and the thickness measurements in the outer ring are interpolated from the line scans. Upper right black and white image is the video scan image showing the position of the six line scans used for the fast macular map. (B) White lines not following the retinal boundaries will be inaccurate in CRT measurements. Note that the white line inaccurately traces the inner and outer retinal boundaries: CRT measurement is 391 µm, about 40 µm greater than the accurately traced map.

If the OCT boundary tracings are inaccurate, the algorithm calculation will also be inaccurate (Fig. 15.2B) (see Chapter 21). For this reason, OCT technicians must identify the appropriate demarcation boundaries within the image to ensure that the thickness measurements are accurate. Technicians should repeat the fast macular map until all six scans overlap in the fovea and are correctly traced.

Fast macular scans produce both a quantitative measurement of the CRT and a qualitative colored topographic retinal thickness map. The topographic map is a graphic representation of the numeric data acquired in the six line scans. Centrally, the retinal thickness should be accurate due to the overlapping of the six data points. Points near the perimeter of the map between the line scans are interpolated from available data and not directly measured with the OCT-3. Quantitative data for peripheral macular thickness are also provided from the interpolation, but caution should be used considering the methods. The reliability of the map has been evaluated.[42–44]

Normal 1-mm central retinal thickness is generally between 200 and 240 μm. While most anti-VEGF therapies strive to "dry" the retina and be free of excess thickness as represented by cystic changes and subretinal fluid, the central retinal thickness can be less than 200 μm or thinner than a normal retina. Values of 170 μm or less may represent a pathologically thinned central macula. Analyses of the CRT 1-mm data and the topographic map may explain poor vision following anti-VEGF therapy by revealing retinal atrophy despite apparently "good" macular anatomy with a normal foveal contour free of cystic spaces, subretinal fluid, pigment epithelial detachment (PED), or scarring. Correlations between CRT and visual acuity are variable and are likely influenced by which layers of the retina are atrophic. Future generations of OCT will provide finer detail of the retinal layers, particularly the photoreceptor layer, and allow a better understanding of the relationship among retinal thickness, anatomy, and visual acuity.

Radial Line Scans: Following the Fluid

Optical coherence tomography also provides important qualitative information about the fluid in the macula and its response to anti-VEGF therapy. In radial lines mode, six high-resolution scans are acquired at 30-degree intervals, each diagonal composed of 512 A-scans. The result is a series of six detailed, cross-sectional images of the central 6 mm of the macula, each at a different angle: 90, 60, 30, 0, 330, and 300 degrees. These images provide qualitative anatomic information about the central macula on a nearly histologic level revealing retinal fluid as cystic alterations in the middle and superficial layers of the retina, pockets of subretinal fluid, or fluid under the RPE as an RPE detachment (RPED). These high-resolution slow scans can theoretically be used to calculate retinal thickness within each section, but are generally not used for quantitative data due to the high likelihood of movement artifact between scans.

Injections of ranibizumab and bevacizumab for neovascular AMD produce a pattern of fluid resolution on OCT that has been studied prospectively. During phase I and II trials of ranibizumab for neovascular AMD, qualitative changes on OCT were observed within weeks following initiation of therapy. The Prospective OCT imaging of Neovascular AMD patients Treated with intraOcular ranibizumab (PrONTO) study was subsequently developed and organized to capture the OCTs of neovascular AMD patients treated with ranibizumab on postinjection days 1, 2, 4, 7, 14, and 30 following the first two treatments. Thereafter, OCTs were obtained monthly for 24 months with additional ranibizumab treatments as needed. To obtain the best qualitative information for the PrONTO study, six radial line slow scans were performed at each monthly visit. Quantitative retinal thickness calculations were taken from fast macular maps as mentioned previously. Technical expertise was important to reliably and reproducibly center all six scans on the foveal center so that sequential comparisons between visits were possible.

The PrONTO study found that macular fluid resolved in a predictable pattern following ranibizumab therapy.[45] First, the cystic changes in the retina resolved and made the largest contribution to a dramatic and rapid reduction in CRT. Shrinkage or complete disappearance of cystic fluid spaces was seen usually following one ranibizumab treatment. Pockets of subretinal fluid were the next component to reabsorb, followed by gradual, incremental resolution of the serous PED component (Figs. 15.3 to 15.5). While most PEDs improved over time, they were variable in their response to ranibizumab treatment and some never completely resolved at 1 year with intermittent ranibizumab therapy.

When monitoring patients on ranibizumab and bevacizumab therapies, trends in vision and OCT data from the PrONTO study should prove to be clinically useful. Changes in OCT occurred within the first day following initiation of ranibizumab therapy and steadily improved (decrease in average CRT and sequential qualitative improvements) through the first 3 to 4 months. Average visual acuity also improved within 2 weeks and steadily increased during the first few months. Generally, changes in OCT preceded changes in vision. Similarly, the recurrence of cystic changes on OCT in a previously fluid-free macula was seen before vision deterioration. Monthly observations from the PrONTO study confirmed the suspicion that once fluid appears, more fluid follows and vision eventually worsens (although vision loss may lag a few months). With this information, it makes sense to re-treat with an anti-VEGF agent as soon as fluid first reappears in the macula or just before the fluid is predicted to reappear based on prior observations.

Some patients present clinical challenges when sequential treatments with ranibizumab or bevacizumab do not improve macular anatomy on OCT at monthly intervals. One possibility is that the improvement on OCT is short-lived, and may be obvious 1 week after an injection, but rebounds quickly over the ensuing 3 weeks, so little change is observed if only the monthly scans are compared. If no change is observed even at 1 week after an injection, then the OCT scans should be

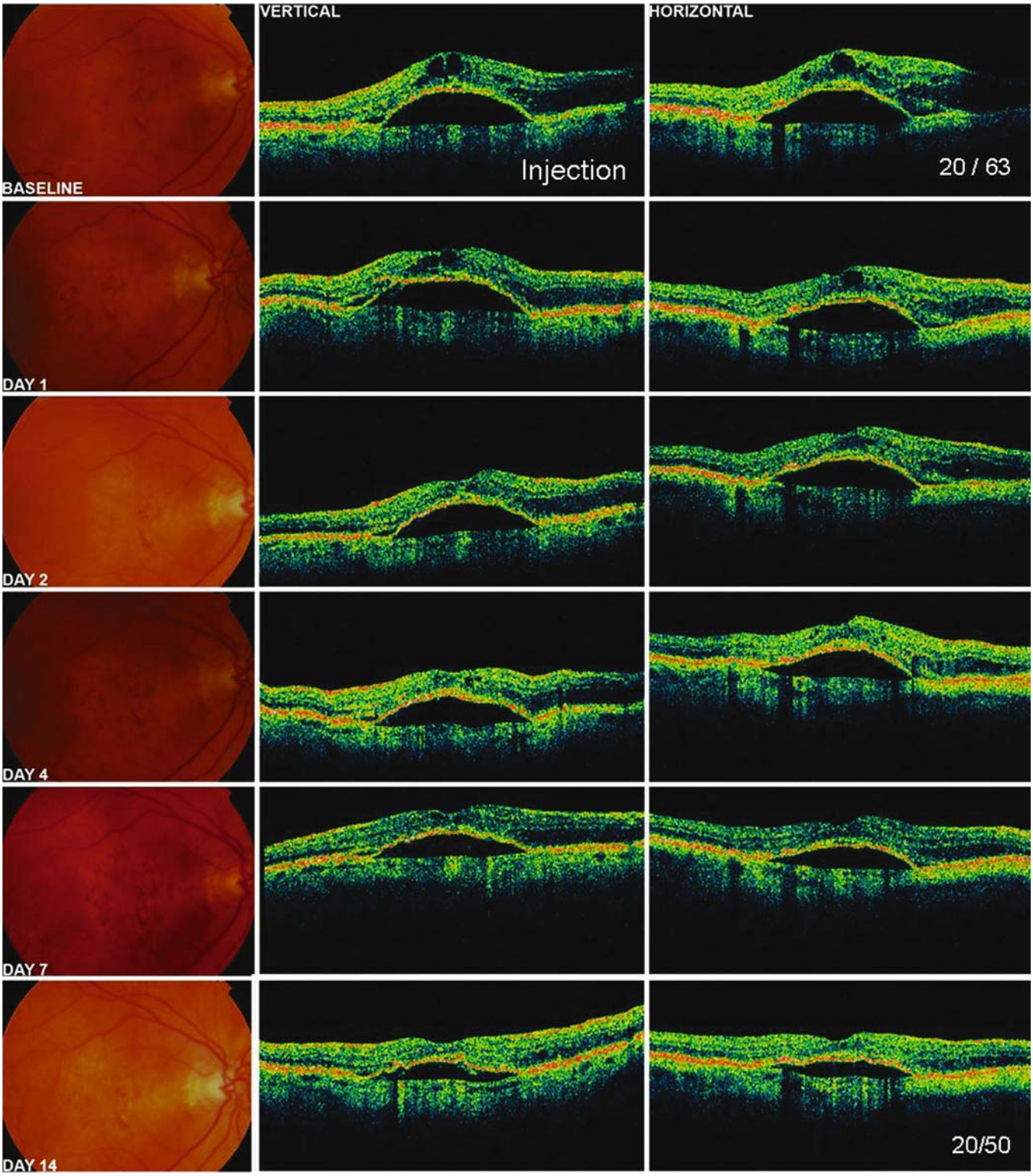


FIG. 15.3. A 90-year-old woman with treatment-naive new diagnosis of neovascular age-related macular degeneration (AMD) involving the fovea of the right eye. Baseline visual acuity is 20/63 (59 letters). Patient receives initial 3-month injections and requires re-treatment according to the PrONTO protocol at months 7 and 12. Optical coherence tomography (OCT) images from baseline through day 14 demonstrate rapid reduction in cystic edema, followed by subretinal fluid and lastly pigment epithelial detachment (PED) after initiation of Lucentis therapy.

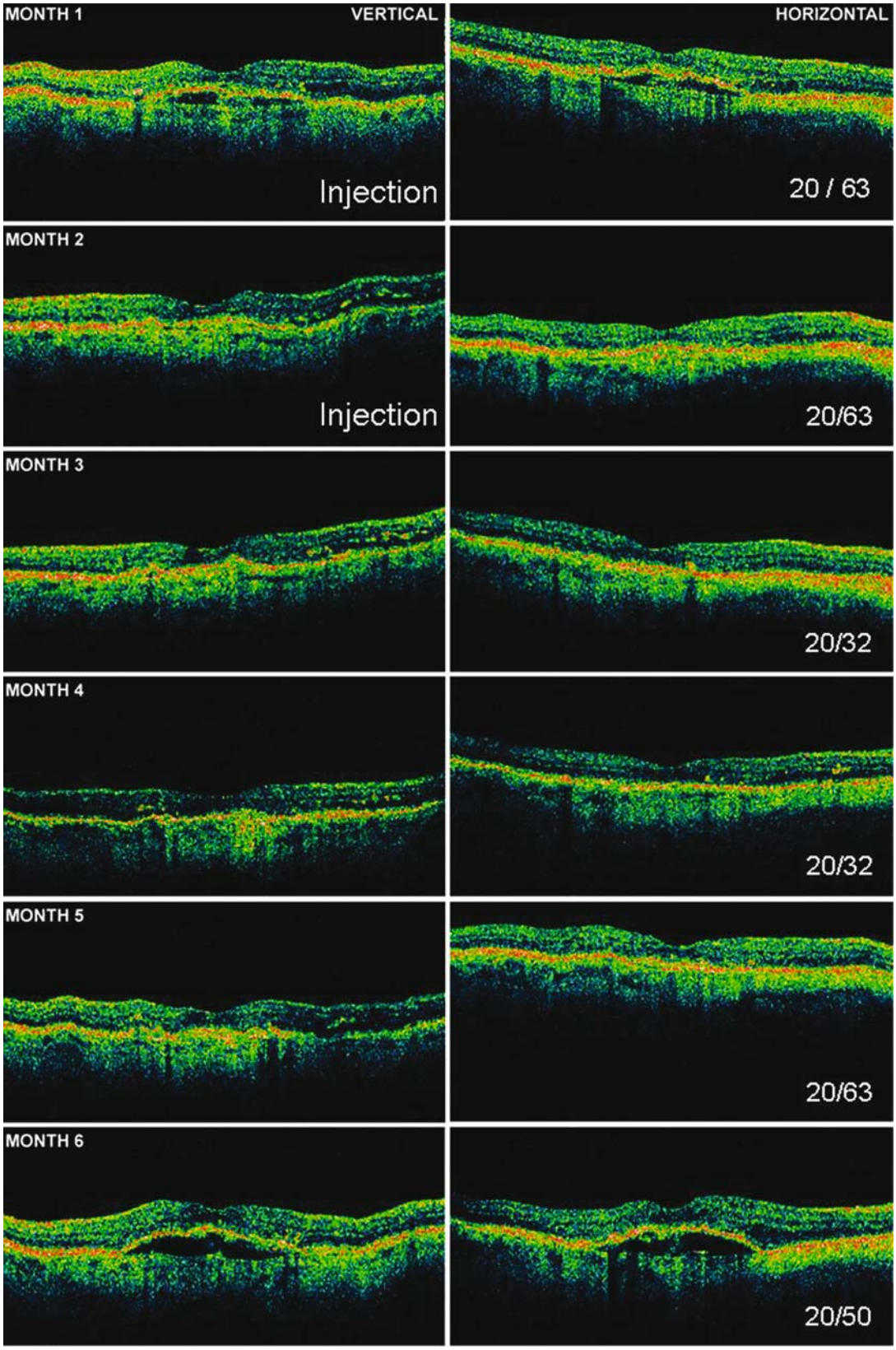


FIG. 15.4. Same patient as in Figure 15.3. Optical coherence tomography composite from months 1 to 6 demonstrates resolution of macular edema through month 3 with consecutive injections and gradual reaccumulation of fluid at month 6.

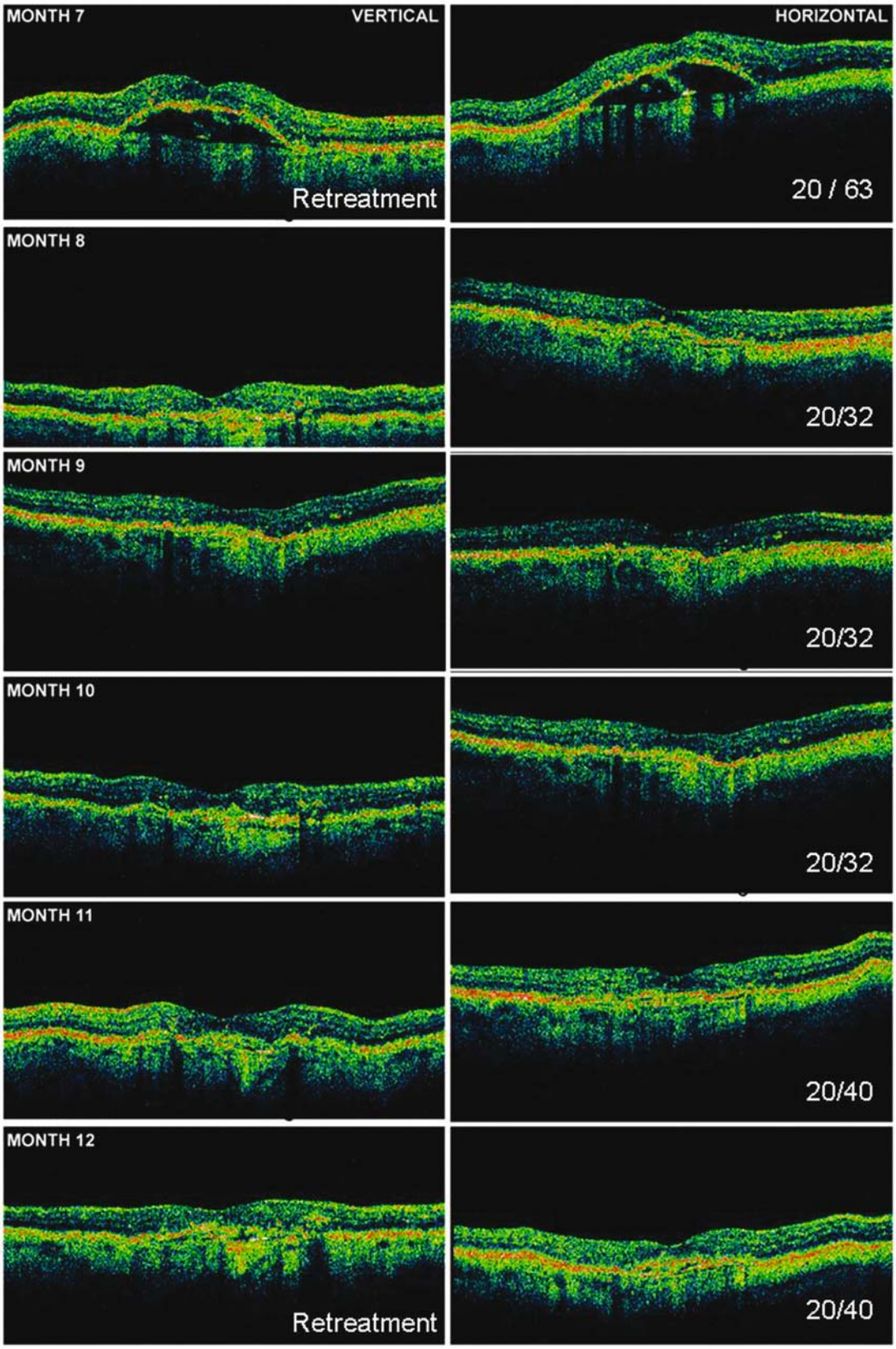


FIG. 15.5. Same patient as in Figures 15.3 and 15.4. Optical coherence tomography composite from months 7 to 12 with further increased macular edema at month 7, and resolution of the macular edema at month 8 following re-treatment. Patient re-treated again at month 12 for >5 letter decrease in vision associated with macular fluid on OCT.

evaluated for confounding causes of increased retinal thickness such as vitreomacular traction or an epiretinal membrane. The OCT characteristics of each are beyond the scope of this chapter (see Chapter 16).

Errors associated with the placement of line scans were potential confounding variables when evaluating PrONTO patients, and caution was needed when using qualitative OCT information in a sequential fashion. Variability in the placement of each diagonal scan may result in an apparent qualitative change between visits where no change actually exists. For example, a radial line scan that is incorrectly centered can miss a pocket of subretinal fluid that was present previously, resulting in the misdiagnosis of a fluid-free macula and therefore can lead to the inappropriate cessation of therapy. To prevent this possibility, OCT technicians must learn to identify the appropriate center of the macula. Unfortunately, using current OCT technology, the technician's job is made even more difficult by having only an indistinct, low-contrast, black-and-white video image of the macula to guide positioning (see Figs. 15.3 to 15.5). This is particularly problematic when the patient's vision is poor and the macula is distorted with fibrosis or fluid. For this reason, landmarks such as the optic nerve, the retinal vessels, or notable scars or pigment play a crucial role in identifying the fovea. Future OCT technology will help resolve these issues, but until then it is essential for the retina specialist to play an active role in training OCT technicians and reviewing the scans prior to accepting any changes in CRT measurements or macular fluid between visits.

Fluorescein Angiography in the Era of Optical Coherence Tomography and Anti–Vascular Endothelial Growth Factor Therapy

The question has been inevitably raised as to how OCT compares to established imaging modalities. Since the 1960s, FA has become the gold standard for the diagnosis and monitoring of AMD, diabetic retinopathy, vascular occlusive disease, and macular edema from a myriad of causes. Several studies have compared FA and OCT, and both advantages and disadvantages of each have been revealed. Fluorescein angiography benefits from decades of use and comprehensive understanding, relative ease of reproducibility, and the dynamic nature of fluorescein leakage or staining over time. However, while FA is relatively safe, it is an invasive procedure with a low but potentially life-threatening risk due to anaphylaxis. Also, in eyes with significant retinal/macular scarring it is challenging to differentiate staining from leakage. On the other hand, OCT is a static imaging modality, but it is a fast, noninvasive procedure that provides structural images of the retina.

The role of FA for AMD treatment is now shifting as the noninvasive, faster technique of OCT becomes an imaging standard. In clinical practice, a wide spectrum exists in current use of FA versus OCT among retinal specialists: some continue to image with FA regularly while others have nearly abandoned the technique. At a minimum, a baseline FA is appropriate to confirm the diagnosis of neovascular AMD. Fluorescein angiography is also appropriate to repeat in cases of unexplained vision loss and poor response during ranibizumab therapy. Fluorescein angiography is thought to be the gold-standard for establishing a particular cause of unexplained vision loss in AMD–the RPE tear. Tears of the RPE, generally following the presence of a PED, are occasional sequelae of neovascular AMD. While impending or early tears of the RPE may be recognized clinically or by using OCT (e.g., attenuation or corrugation of the RPE/Bruch's complex), FA remains the standard for establishing this diagnosis once a tear of the RPE has evolved. However, OCT is generally the most useful tool for following the fluid and for revealing other causes of vision loss such as atrophy of the photoreceptor outer layer, vitreomacular traction, or epiretinal membrane.

Optical Coherence Tomography in Antiangiogenic Therapy for Retinal Vein Occlusion

Vascular endothelial growth factor is believed to play a role in the increased vascular permeability that causes impaired vision from macular edema in retinal vein occlusions. Off-label bevacizumab has also been used for the treatment of branch and central venous occlusions of the retina to achieve short-term gains in visual acuity and improvements in retinal anatomy.[11,22,23,28,46] Trials are also underway to evaluate ranibizumab in retinal edema from venous occlusions. Optical coherence tomography findings in retinal vein occlusions may include an increase in retinal thickness, cystic changes, and pockets of subretinal fluid, but not pigment epithelial detachments. Interpretation of OCTs for antiangiogenic therapy in vascular occlusions may be undertaken in a similar manner to neovascular AMD. Comparisons may be made between visits of reliable central thickness measurements and qualitative changes in the retinal appearance. Gradual reductions in the edema should be observed following ranibizumab or bevacizumab therapy, and this edema may recur at various time points after monthly therapy is discontinued.

Optimizing Optical Coherence Tomography Information: The Importance of Technician Skill

Technical expertise is required to obtain high-quality OCT images that are reliable for interpretation. Rapid improvements can be seen in the macula following anti-VEGF therapy, but true change must be distinguished from artifacts associated with scan placement or unreliable thickness calculations.

Optical coherence tomography retinal thickness scan modes perform differently depending on AMD severity,[47] and incorrect delineation of the outer and inner boundaries may occur with the automated retinal thickness measurement tool.[48] These OCT scan artifacts that can adversely affect retinal thickness measurements and topographic maps are surprisingly common.[49] Therefore, good technical skill is crucial to using OCT as a tool in anti-VEGF therapy.

Fluorescein angiography requires the fine skills of a photographer, but macular OCT demands the reflexes of a video gamer. Optical coherence tomography images are acquired as a laser beam repeatedly scans the retina, and when a quality scan has been taken, the technician has only a moment to "capture" the scan with the click of a button. Slower high-resolution radial line scans require approximately 1 second for each scan. Faster low-resolution scans for macular thickness calculations require about 0.5 seconds apiece.

An optimal OCT technician is both well trained to understand macular anatomy and sufficiently dexterous to capture the image at the correct moment. Slow reflexes or an inability to recognize macular anatomy will produce inferior data. Although the OCT has internal algorithms to correct mild to modest fixation or movement errors, significant deviations cause inaccuracies. Obtaining an image from a patient with a Parkinson's tremor and poor central fixation from AMD requires the ability to diligently chase the fovea while capturing images.

Future Directions

As OCT imaging technology evolves with spectral-domain technology, faster scanning along with higher-resolution images and improved thickness algorithms will result in better, more reliable images and thickness measurements. As this technology improves, the importance of OCT for elucidating and following macular diseases will only be enhanced along with its role in monitoring pharmacologic therapies.

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