Current Management of Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) remains a leading cause of blindness worldwide. The assessment and management of patients with this condition has evolved in the last decades. In this chapter, current standards for diagnosis, follow-up, and treatment of patients with AMD are reviewed and summarized. Namely, we highlight how current assessment has moved from conventional ophthalmoscopy and fluorescein angiography testing to a multimodal approach, and its important advantages. Alternatives to visual acuity for functional assessment of patients with AMD are also presented. Regarding strategies for follow-up and treatment, we provide specific information for the different stages (i.e., early, intermediate, and late) and forms (for example, choroidal neovascularization and geographic atrophy) of AMD. Specifically, we discuss the relevance and options for self-monitoring and non-pharmacological interventions. Additionally, a summary of the important trials (both on exudative and non-exudative AMD) that have helped inform clinical practice is provided, including data on antiangiogenic agents currently available, and outcomes of the different regimens that have been studied. The influence of advances in imaging on treatment strategies is also discussed.

In summary, this chapter is a resource for all clinicians engaged in providing *state of the art* care for patients with AMD, and can help improve diagnosis, management, and outcomes of individuals with this blinding condition.

Keywords

Age-related macular degeneration · Diagnosis · Disease management · Choroidal neovascularization · Geographic atrophy · Intravitreal injections · Office visits · Optical coherence tomography · Photodynamic therapy · Visual acuity

12.1 Current Standards for Diagnosis and Assessment of Non-Exudative AMD

Age-related macular degeneration (AMD) has historically been diagnosed based on a dilated fundus exam, and this remains the gold standard. All current, validated AMD classification schemes are based on color fundus photographs (CFP). Multiple grading systems have been proposed, but there is no universal consensus. The

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most widely accepted grading systems include the Age-Related Eye Disease Study (AREDS) classification scheme [1] and severity scale [2], the International Classification [3], and, more recently, the clinical classification developed by the Beckman Initiative [4]. These classifications differ in the criteria used to define the presence of AMD, and the early and intermediate stages of the disease (i.e., drusen number and sizes). These differences have an impact both on clinical practice and on research. For example, the absence of a clear definition of when AMD is present (versus normal aging) is one of the reasons for the failure to diagnose AMD in an important number of cases. A recent study [5] looked at a group of adults 60 years or older considered to have normal macular health in both eyes according to a dilated eye examination by primary care ophthalmologists and optometrists. The authors found that approximately 25% of these eyes had macular characteristics consistent with AMD, as assessed by fundus photography and trained graders. A clear and unified definition of AMD, and a single standard and accepted classification system, would facilitate the diagnosis of this condition, patients' follow-up, and assessment of outcomes. The implementation of retinal imaging modalities in primary eye care settings, as well as the ongoing development of artificial intelligence applied to images of patients with AMD [6, 7], could also contribute to improve the current underdiagnosis of this condition.

The hallmark findings of non-exudative AMD are macular drusen and focal pigmentary changes, which are present across all stages and forms of AMD [1]. Classic drusen are histologically located between the retinal pigment epithelium (RPE) and Bruch's membrane, and appear as focal, whitish yellow excrescences deep to the retina. In general, drusen are considered by their size. They can be round and discrete, measuring less than 63 μm (small drusen); medium-sized drusen, 63 to less than 125 μm; and soft, which are ill defined, with non-discrete borders, measuring 125 μm or greater [1]. Small or hard drusen are commonly identified in many populations, and do not carry an increased risk for the development of neovascularization [8]. Medium-sized drusen carry a low risk of developing late AMD [9]. In contrast, large, soft, confluent drusen are age-related and associated with AMD and a higher risk for developing advanced AMD [9]. Focal pigmentary changes also have been associated with an increased risk of developing soft drusen and geographical atrophy [9, 10].

Advances in imaging over the years have enabled a greater understanding of disease pathophysiology and have offered important diagnostic value. Among available imaging modalities, optical coherence tomography (OCT) is one of the most widely used, and has served as an essential adjunct in monitoring non-exudative AMD [11–13]. OCT is a non-invasive imaging method capable of providing cross-sectional images of the retina, RPE, and choroid. The initial devices were time-domain and had limited resolution capacity. However, spectral-domain OCT, now widely used worldwide, provides high-quality and high-resolution imaging, and thus has a crucial role not only in the initial diagnosis and prognostic assessment of patients with AMD, but also in follow-up [14]. For example, OCT enables detection of classic drusen, changes in their overall volume, as well as evaluation of retinal and RPE thickness both qualitatively and quantitatively (automated algorithms for quantification are available with the Cirrus OCT, Carl Zeiss Meditec, CA, USA). Additionally, OCT has enabled clinicians and researchers to identify lesions of prognostic value. Examples include subretinal drusenoid deposits (SDD) and outer retinal tubulations. SDD [15, 16] have been proposed as an independent risk factor for AMD progression [17]. SDD can also be identified with other imaging modalities, such as infrared and fundus autofluorescence [18, 19], but spectral-domain OCT has the highest sensitivity (95%) and specificity (98%) to identify these deposits [20]. Outer retinal tubulations, identified on OCT as a circular or ovoid hyperreflective band around a hyporeflective core located in the outer nuclear layer [21], appear in cases of advanced disruption of the outer retina, but have been associated with a slower rate of enlargement of geographic atrophy (GA) lesions [22]. Importantly, in eyes with neovascularization, the

hyporeflective lumen of these lesions may be misdiagnosed as intraretinal or subretinal fluid. Their recognition is important to avoid unnecessary treatment. Other qualitative and quantitative OCT features, such as ellipsoid zone disruption, drusenoid RPE detachment, or RPE drusen volume, have also been suggested as potential OCT biomarkers for risk of AMD progression to advanced AMD [23–25].

The assessment of geographic atrophy, one of the forms of late AMD, has also changed over time. Classically, GA has been defined based on CFP, where it is seen as one or more well-delineated areas of hypopigmentation or depigmentation due to absence or severe attenuation of the underlying RPE [1]. The large, deep choroidal vessels are usually readily visualized in these areas. Different classification schemes consider different criteria in terms of size and foveal involvement, as recently reviewed by the Classification of Atrophy Consensus (CAM) group [26], a consortium of retina specialists. However, advances in retinal imaging technology, including high-resolution OCT, have markedly improved the detection and study of GA morphology. The CAM group recently provided recommendations on the use of imaging modalities to detect and quantify atrophy [27]. The authors highlighted that the imaging protocols to detect, quantify, and monitor progression of atrophy should include CFP, as well as confocal fundus autofluorescence (FAF), confocal near-infrared reflectance (NIR), and high-resolution OCT volume scans. Despite being originally developed for clinical trials, these recommendations can be easily translated to clinical practice. Currently, FAF imaging together with OCT are the most commonly used modalities [27]. Figure 12.1 presents an example of progression of GA demonstrated using FAF images.

12.2 Current Standards for Diagnosis and Assessment of Exudative AMD

The late forms of AMD include geographic atrophy (GA), and choroidal neovascularization (CNV), also known as "exudative AMD." Both manifestations are not mutually exclusive. GA can develop in eyes with CNV effectively treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections; and CNV can appear in eyes with pre-existing GA [28, 29].

In addition to funduscopy, fluorescein angiography (FA) is the gold standard to diagnose and classify CNV [30]. Classically, three types of CNV have been described: (i) type 1 CNV, also known as occult choroidal neovascularization, which refers to new blood vessels that proliferate underneath the RPE—on FA, it presents as a fibrovascular pigment epithelial detachment (PED: an area of irregular elevation of the RPE, often with stippled hyperfluorescence present in the midphase of the angiogram and leakage or staining by the late phase) or late leakage from an undetermined source (speckled hyperfluorescence with dye pooled in the subretinal space in the late phase); (ii) type 2 CNV, or classic CNV, which is characterized by the development of new blood vessels between the neurosensory retina and the RPE—on FA, it is characterized by a bright, often "lacey," early hyperfluorescence exhibiting prominent leakage in the late phase; and (iii) type 3 CNV, also known as retinal angiomatous proliferation (RAP), which is characterized by the formation of a retinal–retinal anastomoses, which then extends beneath the neurosensory retina to become subretinal neovascularization. Indocyanine-green angiography (ICGA) provides additional information on choroidal vasculature [31], and it is recommended when polypoidal choroidal vasculopathy (PCV) is suspected [32]. Despite the ongoing debate [32], PCV is considered a variant of exudative AMD, which is characterized by the presence of orange-red nodules and serosanguinous pigment epithelial detachments on ophthalmoscopy. ICGA enables the visualization of polyps and branching vascular networks in this condition, which are often difficult to detect on FA.

Regardless of the form of neovascularization, OCT is currently considered an important adjunct to FA and ICGA, especially to monitor the presence of intraretinal and subretinal fluid over time.

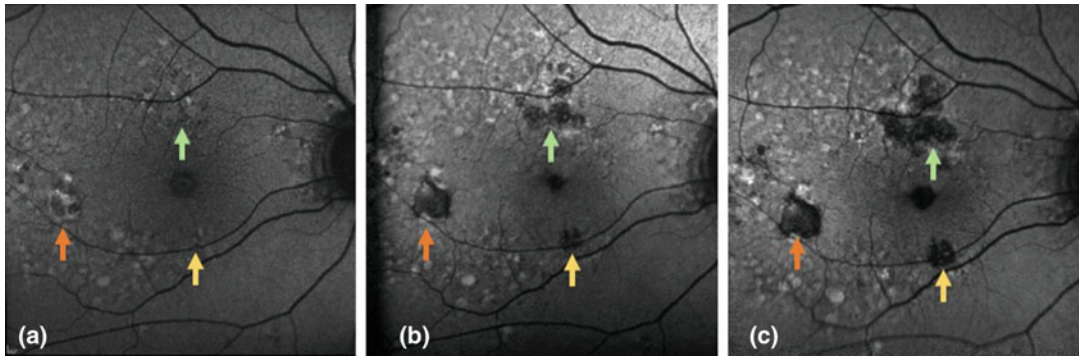

Fig. 12.1 Fundus autofluorescence images of a right eye with progression of geographic atrophy over 3 years. As shown, initial areas of hypo-autofluorescence increased in size during this time period (marked as colored arrows). (**a**) Baseline, (**b**) 2 years later, (**c**) 3 years after baseline

Indeed, data suggest that at least in the USA several clinicians currently rely solely on clinical examination and OCT to determine whether a treatment regimen is adequate in controlling disease activity [33]. Since the advent of drugs that inhibit vascular endothelial growth factor (VEGF), one of the strategies for following eyes with wet AMD has been to use OCT to guide treatment frequency based on the status of exudation in the macula.

More recently, OCT angiography (OCTA) has also been used for detailed qualitative and quantitative characterization of CNV in AMD [34, 35]. OCTA is commercially available both for spectral-domain and swept-source devices, and relies on blood flow detection based on motion contrast. Compared to FA, its greatest advantage is being non-invasive; however, it does not allow for the identification of leakage and projection artifacts can occur [36]. The full clinical value and optimal application of OCTA are still being defined [27], but it has been suggested that it enables more distinct characterization of neovascular patterns than FA, since there is less light scattering and less obscuration by overlying subretinal hemorrhages or exudation. Another interesting application includes the study of quiescent neovascular membranes, which are defined as CNV in the absence of exudation. The clinical and prognostic value of quiescent CNV remains to be established. Namely, there is still no consensus on the best approach to manage these lesions, especially if their size is increasing despite the absence of exudation. Recently, de Oliveira Dias et al. suggested that risk of exudation is greater for eyes with documented subclinical CNV on OCTA, compared with eyes without detectable CNV [37].

It is important to note that individuals with neovascularization in one eye have increased risk of developing it in the fellow-eye, so close follow-up may be warranted [38, 39]. This can include more frequent clinic visits for dilated fundus examination and retinal imaging, or by encouraging vigilant home monitoring, as described later in this chapter.

12.3 Functional Assessment of AMD Patients

Visual acuity (VA) is currently the most widely accepted and universally used functional outcome measure for AMD, both in clinical practice and clinical trials or observational studies. However, VA has well-recognized limitations in characterizing visual impairment of AMD, especially early in the course of disease [40]. VA loss typically occurs late in the disease course [41], making it a less useful measure of retinal function in early and intermediate AMD. Therefore, other

functional outcome measurements have been explored [42]. These include contrast sensitivity [43], low-luminance visual acuity, photopic or scotopic light sensitivity [44, 45], and dark adaptation (DA) [41]. DA is promising, and there is currently a commercially available U.S. Food and Drug Administration (FDA)-approved device [46]. Studies have shown that DA can differentiate AMD from healthy eyes, and has correlations to the different stages of AMD based on conventional CFP classification schemes [41, 46, 47]. More recently, an association between AMD features identified on OCT and time to dark-adapt has also been described, including the presence of SDD and ellipsoid changes [48]. Figure 12.2 shows an example of an eye with SDD and prolonged time to dark-adapt.

12.4 Management of Non-Exudative AMD

There are currently no proven therapies for the non-exudative form of AMD or limited options to halt progression from the early/intermediate AMD stages to late disease. Certain behavioral modifications may be beneficial in reducing risk of advanced AMD. Smoking is considered the most important modifiable risk factor for AMD [49–51]. Smoking cessation should be strongly recommended to patients since the risk of developing AMD in individuals who have not smoked for more than 20 years is comparable to the risk in nonsmokers [52]. There is also extensive literature on dietary interventions that may be beneficial [53, 54]. In general, a diet similar to the Mediterranean diet, rich in fruits, vegetables, and fish, is recommended. Other risk factors, such as hypertension or obesity, have also been linked to AMD risk, but available data are inconsistent [53, 55]. Considering the benefit of controlling these risk factors for reduction in cardiovascular risk, patients may be advised to discuss these risk factors and their appropriate management with their primary care physicians.

For patients with intermediate AMD, the dietary supplements studied by the Age-Related Eye Disease Study (AREDS) group are recommended. The initial AREDS trial evaluated the effect of daily oral therapy with high doses of vitamin C (500 mg), vitamin E (400 international units), beta-carotene (15 mg), zinc (80 mg as zinc oxide), and copper (2 mg as cupric oxide), and showed that, in patients with intermediate AMD in at least one eye, the formula was able to reduce the progression to advanced AMD by 25% at 5 years [1]. The AREDS 2 trial followed [56] to investigate the role of omega-3 fatty acids in reducing progression of AMD and whether beta-carotene was necessary for efficacy due to concerns of possible associations with lung cancer in smokers. A new formulation was proposed, where lutein (10 mg) + zeaxanthin (2 mg) were introduced to substitute for beta-carotene. Beta-carotene was associated with a twofold increase in the risk of lung cancer. There was an incremental benefit with lutein and zeaxanthin versus beta-carotene in preventing progression to advanced AMD, especially in persons who had the lowest intake of dietary intake of lutein. When lutein and zeaxanthin were compared with beta-carotene, there was a 25% increased beneficial effect. The currently recommended formulation consists of vitamin C (500 mg), vitamin E (400 international units), lutein (10 mg) + zeaxanthin (2 mg), zinc (80 mg as zinc oxide), and copper (2 mg as cupric oxide). Recently, investigations have been performed to assess whether genotype at certain loci associated with AMD risk may impact benefit from supplementation with the AREDS formula [57–64]. These studies remain controversial and routine genetic testing prior to supplementation has not been recommended or widely adopted. Three independent groups evaluated the data from the AREDS researchers and the data from the non-AREDS researchers and concluded that there was no evidence to support genetic testing prior to initiating supplementation with the AREDS formula [65]. A prospective study would be required to determine whether there in fact is any association between genotype and response to AREDS supplementation.

For all patients with non-exudative AMD, the use of the Amsler grid [66] to assess for new metamorphopsia is recommended. Early detection of neovascular disease remains a priority. It

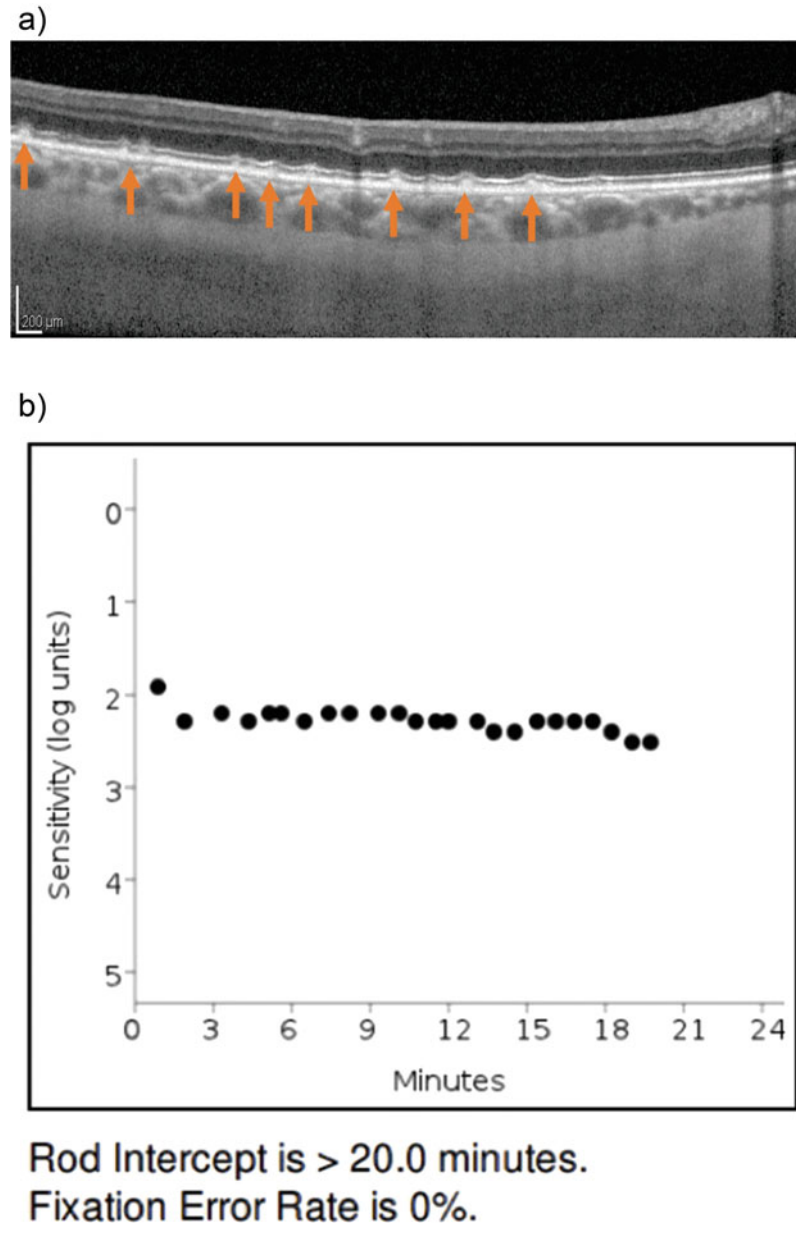

Fig. 12.2 (**a**) Optical coherence tomography showing multiple subretinal drusenoid deposits (orange arrows); (**b**) dark adaptation curve of the same eye, where it is shown that the rod intercept time is not achieved within the test period (20 min, standard available commercial test)

has been shown that treatment of choroidal neovascularization within 1 month of detecting symptoms is more likely to result in better visual outcomes [67]. Several technologies for home monitoring currently exist, including ForeseeHome™. ForeseeHome™ is a self-administered test that uses preferential hyperacuity perimetry to measure visual field defects using 500 retinal data points over 14° of a patient's central visual field. The AREDS Home Monitoring of the Eye (HOME) Study compared visual acuity at the time of choroidal neovascularization diagnosis between 1520 at-risk dry AMD patients who were randomly assigned to use the device plus standard-of-care (self-monitoring with Amsler grid and routine clinic visits) and a control group utilizing standard-of-care alone [68]. Their results showed that patients with

high risk for developing CNV may benefit from frequent and regular home-screenings with highly sensitive technology.

12.4.1 Geographic Atrophy

There is currently no approved treatment to slow or halt the progression of geographic atrophy (GA). One of the most explored potential targets for therapies has been the complement system. Although the pathophysiology of GA is incompletely understood, overactivation of the complement has been implicated in its the pathogenesis [69], and genome-wide association studies [70] have also suggested a central role of the complement system in AMD. Several clinical trials have been performed targeting different complement cascade components. The largest studies conducted to date used lampalizumab, an antigen-binding fragment of a humanized monoclonal antibody that inhibits complement factor D, and failed to show a reduction in GA enlargement as compared to sham during 48 weeks of treatment [71] (Fig. 12.3). Other complement components have also been attempted as potential targets, including with eculizumab, which also failed a phase II trial [72].

Other drugs targeting different pathways involved in GA pathogenesis have been studied and failed to show efficacy. These include attempts to modulate the visual cycle (such as with emixustat; hydrochloride [Acucela]; a small non-retinoid molecule that specifically binds and inhibits RPE65 and its active site, and fenretinide, an oral synthetic derivate of vitamin A), neuroprotection (such as with an implant producing ciliary neurotrophic factor, NT-501), and amyloid beta aggregation (with an anti-amyloid beta monoclonal antibody, GSK933776; GlaxoSmithKline) [72]. Gene and stem cell therapies have also been attempted but remain in their infancy [73, 74].

12.5 Management of Exudative AMD

12.5.1 Photodynamic Therapy

In 2000, photodynamic therapy (PDT) with verteporfin was approved as the first pharmacologic therapy for exudative AMD. It consists of a two-step procedure involving intravenous infusion of verteporfin, a photosensitizing dye that accumulates preferentially in neovascular membranes, followed by dye activation with infrared (689 nm) laser light [75]. This process results in direct cellular injury, including damage to vascular endothelial cells and vessel thrombosis; and it promotes closure of choroidal neovascular complexes, with relative sparing of the overlying retinal structures [76–78].

Two large, prospective, randomized controlled trials led to the approval of PDT for neovascular AMD: the TAP—Treatment of AMD with Photodynamic Therapy Study—Study, and the VIP—The Verteporfin in Photodynamic Therapy Study—Trial [79, 80]. The TAP Study demonstrated lower rates of moderate vision loss through 2 years in patients with predominantly classic subfoveal CNV treated with verteporfin PDT (47%) compared to placebo (62%). For occult with no classic CNV lesions, the VIP Trial showed that verteporfin PDT treatment demonstrated greater efficacy than placebo in preventing moderate vision loss (percentage of eyes losing less than 15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters: 46.2% versus 33.3%) in a 24-month period. Side-effects included hemorrhage, neurosensory detachment, and choroidal infarction.

Currently, antiangiogenic therapy has largely replaced verteporfin PDT therapy as the preferred treatment modality for neovascular AMD as it achieves better visual outcomes. However, verteporfin PDT is still considered in patients with systemic or ocular contraindications for intravitreal administration of antiangiogenic drugs, and it is an important option for the

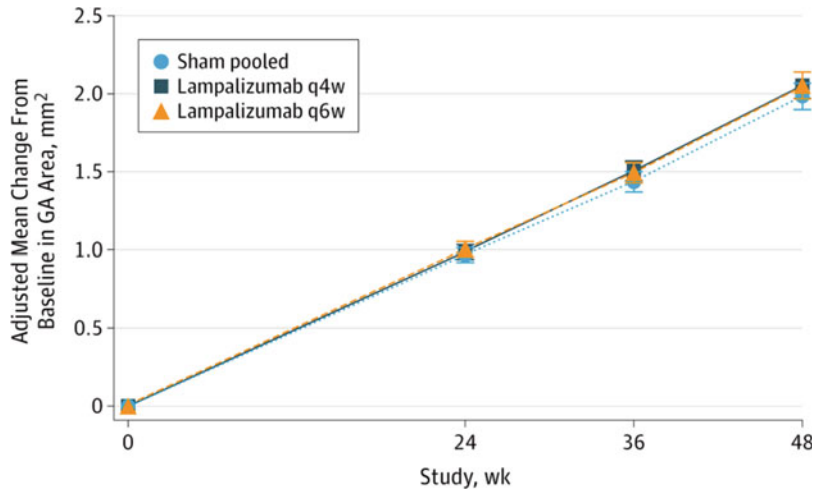

Fig. 12.3 Overall results from phase 3 trials of lampalizumab for geographic atrophy due to macular degeneration. Graph shows adjusted mean change in area of geographic atrophy from baseline to week 48 (measured on fundus autofluorescence imaging). Reprinted with permission from *JAMA Ophthalmol*. 2018 Jun 1;136(6):666–677

treatment of polypoidal choroidal vasculopathy (PCV). Figure 12.4 presents a color fundus photograph and indocyanine-green angiography of an eye with PCV. The EVEREST II trial demonstrated that verteporfin PDT combined with ranibizumab resulted in greater visual acuity improvement (8.3 versus 5.1 letters) than monotherapy with ranibizumab, and complete resolution of lesions with fewer ranibizumab injections [81].

12.5.2 Anti-VEGF Therapies

Vascular endothelial growth factor (VEGF) plays an important role in intraocular neovascularization in a number of conditions. VEGF-A acts via the VEGF receptor 2 (VEGFR2) and is thought to be the main stimulator of angiogenesis and vascular permeability in neovascular AMD [82]. Four different VEGF-A isoforms have been identified in humans as a result of alternative RNA splicing: $VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$ [83]. Among them, $VEGF_{165}$ is the most prevalent in ocular neovascularization processes [84, 85]. In the last decade, anti-VEGF

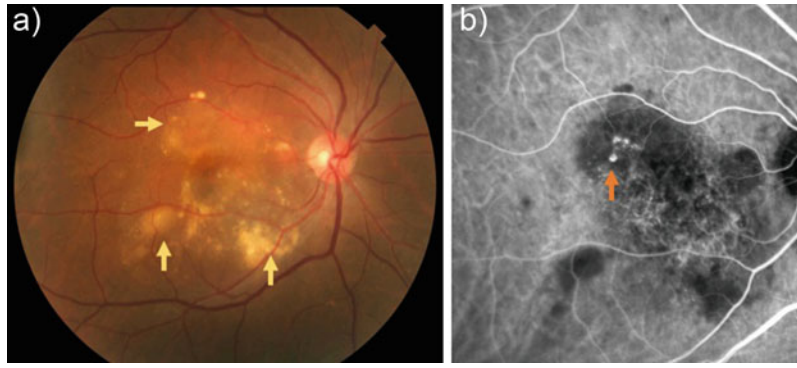

Fig. 12.4 (**a**) Color fundus photograph of a right eye with polypoidal choroidal vasculopathy, where extensive lipid exudation (yellow arrows) is observed in the macular area; (**b**) indocyanine-green angiography of the same eye, where multiple focal areas of hyperfluorescence (i.e., polyps; orange arrows) are seen arising from the choroidal circulation

therapy has become first-line treatment for neovascular AMD. Four major agents have been evaluated and widely used.

(a) *Pegaptanib*

Pegaptanib sodium (Macugen; Eyetech/Valeant Pharmaceuticals) was the first VEGF-A inhibitor approved by the U.S. Food and Drug Administration (FDA) in 2004 for the treatment of neovascular AMD. Pegaptanib sodium is an RNA oligonucleotide ligand (or aptamer) that binds and inhibits $VEGF_{165}$ with high affinity and specificity [86]. Its approval for clinical use was based on two prospective, double-masked, randomized, controlled phase III clinical trials, known as the VEGF Inhibition Study in Ocular Neovascularization (VISION) Study [87]. In these trials, patients with neovascular AMD were randomized to receive intravitreal injections of pegaptanib sodium (0.3, 1.0, or 3.0 mg) or sham injection every 6 weeks for 48 weeks. At 2 years, there was a higher proportion of patients gaining vision for those assigned to 2 years of 0.3-mg pegaptanib than those re-randomized to discontinue pegaptanib after 1 year or receiving usual care [88].

(b) *Ranibizumab*

Ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) was approved by the FDA in 2006 for the treatment of neovascular AMD. Ranibizumab is a 48-kilodalton (kDa) recombinant, humanized immunoglobulin G1 (IgG1) monoclonal antibody fragment (kappa isotype) that binds with high affinity to all isoforms of VEGF-A [89]. FDA approval was based on results from two landmark trials: the Minimally Classic/Occult Trial of Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) [90] and Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD (ANCHOR) [91]. The MARINA trial was a phase 3, randomized, multicenter, double-blind, sham-controlled, 2-year study. Patients with minimally classic or occult CNV secondary to AMD were randomized to receive monthly intravitreal ranibizumab (0.3 or 0.5 mg) or sham injections [90]. Overall, 95% of patients treated with ranibizumab lost less than 15 letters at 1 year compared with 62% of patients receiving sham injections. In addition, visual acuity improved by 15 or more letters in 34% of the 0.5 mg ranibizumab-treated group versus 5% in the sham-injection group at 2 years.

In phase 3, international, multicenter, randomized, double-blind ANCHOR trial, patients with predominantly classic lesions were randomly assigned to monthly intravitreal injections of ranibizumab (0.3 or 0.5 mg) plus sham verteporfin photodynamic therapy (PDT) or to verteporfin PDT plus monthly sham injections. At 1 year, 95% of those treated with ranibizumab and 64% of patients treated with PDT lost fewer than 15 letters compared with baseline [91]. In terms of visual outcomes, 41% of 0.5 mg ranibizumab-treated patients gained 15 or more letters compared with 6% of the PDT group at 2 years [92].

(c) *Bevacizumab*

Bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA) is a 149-kDa full-length humanized, monoclonal IgG1 antibody that binds all isoforms of VEGF-A, and is almost three times the size of the ranibizumab molecule [93]. Bevacizumab was approved in 2004 as first-line therapy for patients with metastatic colorectal cancer, as it was shown to inhibit angiogenesis and tumor growth [93]. The first open-label prospective clinical study using intravenous bevacizumab for neovascular AMD was the Systemic Avastin for Neovascular AMD (SANA) study [94]. Eighteen participants were treated with two or three intravenous infusions of bevacizumab (5 mg/kg) at 2-week intervals. Systemic bevacizumab was associated with a decrease in central retinal thickness of 112 um and a 14-letter gain in visual acuity at 24 weeks. Ten patients developed mild hypertension that was controlled with systemic medications.The use of intravitreal bevacizumab for the treatment of exudative AMD was first described in 2005 in a 63-year-old woman with subfoveal CNV [95]. She received a single intravitreal injection of 1 mg bevacizumab. At 1 week, there was

resolution of subretinal fluid on OCT. This effect was maintained at 4 weeks [95]. Since then, intravitreal bevacizumab has gained widespread acceptance due to its effectiveness, safety profile, and its inexpensiveness compared with other anti-VEGF intravitreal therapies. Large clinical trials such as the Comparison of AMD Treatment Trials (CATT Study) and the Inhibition of VEGF in Age-related Choroidal Neovascularization (IVAN) study also showed that monthly injections of bevacizumab or ranibizumab resulted in approximately the same visual outcomes at the end of 1 and 2 years [96, 97].

(d) *Aflibercept*

Aflibercept (EYLEA, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) is a 115-kDa recombinant, chimeric, decoy receptor comprised of VEGF receptor 1 (VEGFR1) and VEGF receptor 2 (VEGFR2) fused to the Fc portion of human IgG1 [97]. This protein binds VEGF-A, VEGF-B, and placental growth factor (PlGF) and has a 100-fold greater binding affinity for VEGF-A [98]. Aflibercept was approved in 2011 based on the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1 and 2) trials [99]. VIEW 1 and 2 were two phase 3, randomized, double-blind, multicenter, non-inferiority studies that compared ranibizumab with aflibercept in patients with wet AMD. Patients were randomized to four different therapy groups: 2 mg aflibercept every 4 weeks; 0.5 mg aflibercept every 4 weeks; 2 mg aflibercept every 8 weeks; and 0.5 mg ranibizumab every 4 weeks. All treatment regimens were initiated with 3 monthly doses.
These studies demonstrated that 2 mg aflibercept injections administered every 8 weeks following a 3-month loading period had similar improvements in anatomic and visual outcomes to those obtained with monthly ranibizumab injections [99].

(e) *Brolucizumab*

Brolucizumab (Beovu, Novartis) is a 26-kDa, humanized, single-chain antibody fragment that inhibits all VEGF-A isoforms [100]. The HAWK and HARRIER trials were phase 3, randomized, double-masked, multicenter, non-inferiority studies comparing brolucizumab with aflibercept in patients with neovascular AMD. In the HAWK trial, patients were randomized to aflibercept (2 mg) or brolucizumab (3 mg or 6 mg). In the HARRIER trial, patients received either brolucizumab at 6 mg or aflibercept at 2 mg [100]. After 3 monthly loading doses, brolucizumab-treated patients received an injection every 12 weeks with the option to decrease to every 8 weeks at each disease activity assessment. Aflibercept was given at a fixed 8-week interval dose. At 48 weeks, brolucizumab was found to be non-inferior to aflibercept with respect to mean change in visual acuity from baseline (Fig. 12.5). Additionally, central subfield thickness reductions were greater in the brolucizumab arm compared to the aflibercept arm at 16 weeks and 48 weeks [101].

12.5.3 Anti-VEGF Treatment Regimens

In both the MARINA and ANCHOR trials, ranibizumab was administered monthly for 24 months [90, 91]. In routine clinical practice, patient adherence to monthly treatment schedules has proven difficult. There has been great interest in identifying alternative dosing strategies that reduce the number of anti-VEGF injections without compromising visual acuity outcomes. These alternative dosing regimens include a pro re nata (PRN) regimen, where retreatment is given at monthly visits if there is fluid accumulation or hemorrhage, and a "treat-and-extend" regimen where treatment intervals are lengthened until signs of recurrent fluid.

(a) *As-Needed Treatment*

In as-needed (PRN) treatment regimens, injections are given based on the presence of active neovascular AMD. The PRN dosing requires the same number of visits as the fixed-monthly interval, but the regimen reduces the injection burden by three to four injections in a year. Monthly visits are required to determine the need for retreatment.

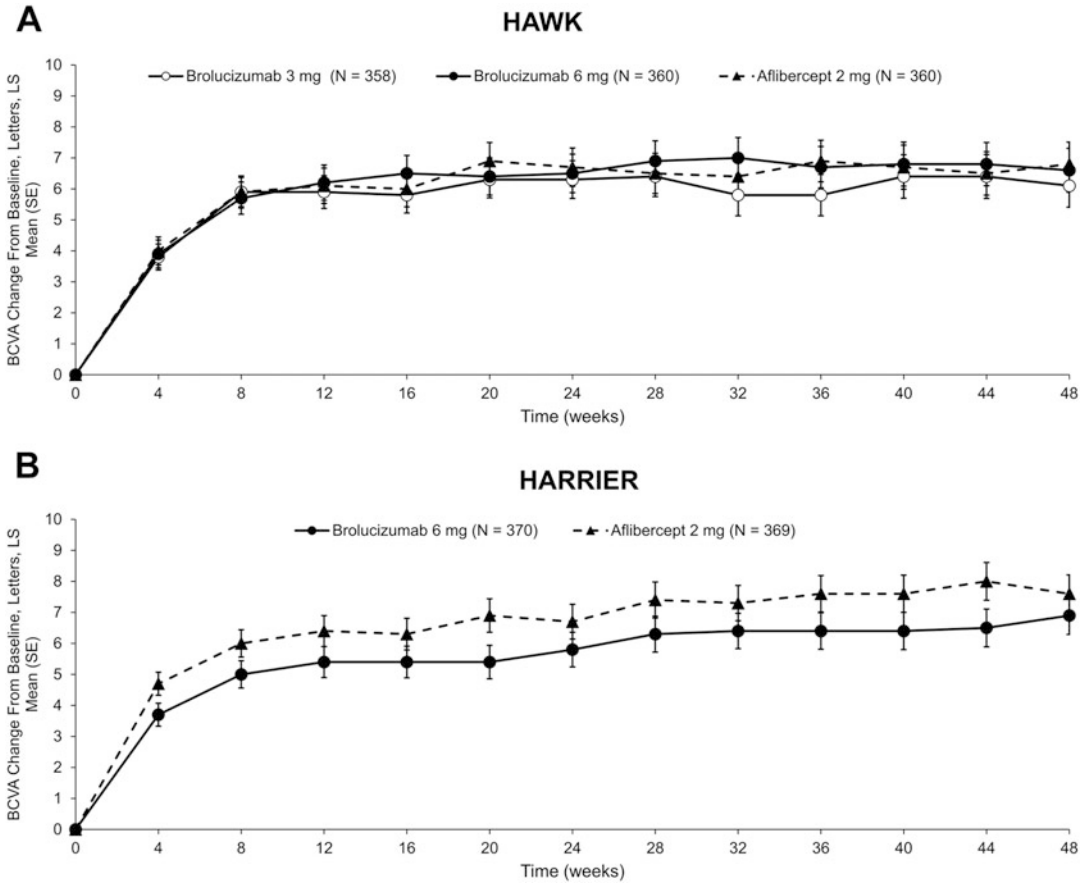

Fig. 12.5 Visual acuity results from a phase 3 trial of brolucizumab versus aflibercept for neovascular age-related macular degeneration (HAWK and HARRIER). The graph shows least-square mean best-corrected visual acuity (BCVA) change from baseline (number of letters) for aflibercept and brolucizumab. Reprinted from *Ophthalmology*. 2019 Apr 12. pii: S0161–6420(18)33018–5. doi: https://doi.org/10.1016/j.ophtha.2019.04.017 with permission

Early prospective studies investigating a PRN approach included the Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Lucentis (PrONTO) study [102] and the Study of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (SUSTAIN) study [96]. In both studies, patients received three, monthly, intravitreal injections of ranibizumab, followed by monthly office visits. Retreatment was performed if any of the following criteria was met: loss of visual acuity of greater than five letters, increase of at least 100 μm in central macular thickness on OCT, or new hemorrhage.

During the second year in PrONTO, the retreatment criteria were amended to include retreatment if there were any qualitative increase in the amount of fluid detected on OCT. At 24 months, patients required a mean of 9.9 injections and median of 9.0 injections (compared with 24 injections in MARINA and ANCHOR) [102]. In addition, 17.5% of patients did not require further treatments after the initial 3 monthly injections. Mean BCVA outcomes were similar to MARINA and ANCHOR at 24 months.

The SUSTAIN trial was a 1-year, phase 3, multicenter study performed in Europe and Australia evaluating as-needed dosing of ranibizumab in patients with CNV secondary to AMD [96]. While BCVA improved at month 3 (+5.8 letters), visual acuity declined slightly between months 3 and 6, but had a mean improvement of 3.6 letters at month 12. Both studies showed that acceptable patient outcomes can be achieved with an as-needed treatment regimen.

The Comparison of AMD Treatment Trials (CATT Study) was a multicenter, non-inferiority, randomized trial of neovascular AMD patients aged 50 years or older comparing the safety and efficacy of bevacizumab versus ranibizumab on a PRN dosing or monthly fixed dosing regimen [96]. The study's primary outcome was mean change in visual acuity at 2 years. All patients received treatment on initial visit and were followed monthly thereafter for 2 years. After 1 year, patients who were assigned to the monthly treatment groups were re-randomized to monthly or as-needed treatment without change in their drug assignment. At 2 years, a subtle difference emerged with the ranibizumab group gaining more letters than the bevacizumab group. The monthly administration of ranibizumab and bevacizumab led to an average gain of 8.8 letters and 7.8 letters, respectively, while the as-needed regimen led to gains of 6.7 letters and 5.0 letters ($p = 0.046$) [103]. In addition, monthly dosing of either treatment did not protect against vision loss when switched to as-needed dosing in the second year. Patients who switched to as-needed dosing after 1 year of monthly dosing had a mean loss of 2.2 letters ($p = 0.03$) and an increase in subretinal fluid [103].

The Inhibition of VEGF in Age-related Choroidal Neovascularization (IVAN) study was a similar study in the United Kingdom that randomized patients to 0.5 mg ranibizumab or 1.25 mg bevacizumab monthly or as-needed dosing [104]. There were no significant differences found in BCVA between bevacizumab and ranibizumab or between continuous and discontinuous treatments.

(b) *Treat-and-Extend*

The treat-and-extend regimen involves extending intervals between treatments as long as there is no macular fluid present. If fluid is present, the interval between treatments is typically shortened. The goal of treat-and-extend is to find the optimal treatment interval that stabilizes visual acuity and controls disease activity.

The Lucentis (ranibizumab) Compared to Avastin (bevacizumab) Study (LUCAS) was the first prospective, randomized, multicenter trial to use a treat-and-extend protocol [105, 106]. This study ($n = 432$) compared the safety and efficacy of bevacizumab versus ranibizumab for neovascular AMD through 2 years. Both arms were given injections every 4 weeks until there was inactive disease with no induction phase. The minimum treatment interval was 4 weeks and the maximum treatment interval was 12 weeks. After 1 year of treatment, this study found that treat-and-extend with ranibizumab or bevacizumab resulted in mean increases in BCVA of 8.2 and 7.9 letters, respectively. This was comparable to the visual acuity gains in the CATT study of 8.5 and 8.0 letters, respectively, at 1 year [106]. Ranibizumab was found to be equivalent to bevacizumab, with 6.6 and 7.4 letters gained, respectively at 2 years.

More recently, the Treat and Extend (TREND) study, was a 12-month, randomized, multicenter, intervention study to compare the effects of treat-and-extend versus monthly ranibizumab regimens on best-corrected visual acuity in patients [107]. The treatment intervals were extended by 2 weeks at each visit if there was no disease activity with a maximum of a 12-week treatment interview. The study, which included 650 treatment-naive AMD patients aged 50 and older, determined that the 2 treatment regimens resulted in similar visual acuity outcomes and the treat-and-extend regimen resulted in fewer injections (8.7 versus 11.1; Fig. 12.6).

Over the long term, repeated anti-VEGF injections may increase the chance of ocular complications. Infectious endophthalmitis remains one of the most devastating complications of intravitreal injections. In

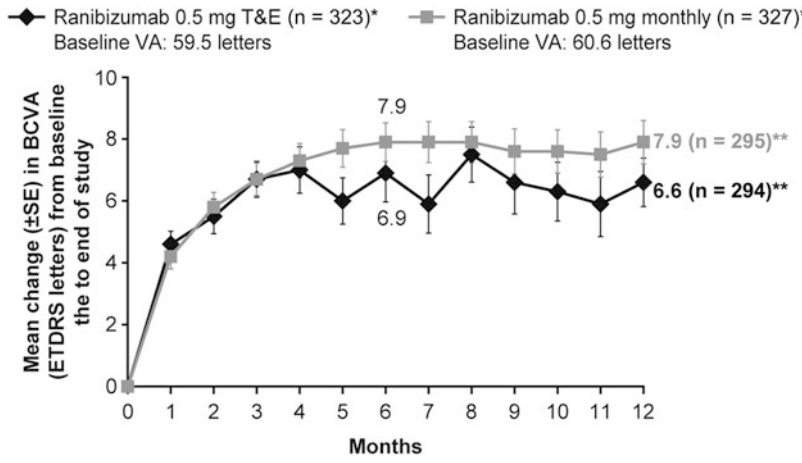

Fig. 12.6 Visual acuity results from the Treat-and-Extend versus Monthly Regimen in Neovascular Age-Related Macular Degeneration (TREND) study demonstrating non-inferiority of ranibizumab administered on a treat-and-extend regimen compared to monthly dosing. Reprinted from *Ophthalmology* 2018;125:57–65 with permission

multicenter clinical trials, the incidence of endophthalmitis has been reported to range from 0.016% to 1.6% [108–110]. Studies have also suggested that chronic anti-VEGF therapy may be associated with the development of macular atrophy, but whether this is part of the natural history of the disease or is treatment-related remains unclear [111]. In addition, long-term or sustained rise in intraocular pressure (IOP) after anti-VEGF injections has been reported, with a greater number of intravitreal injections being associated with a higher risk for sustained IOP elevation [112, 113].

(c) *Tachyphylaxis and Need to Switch Agents*

Most patients with exudative AMD require repeated intravitreal injections. The SEVEN-UP study reported the long-term, 7-year outcomes of 65 AMD patients that had originally enrolled in the ANCHOR, MARINA, and HORIZON studies [114]. Approximately, 68% of patients had active disease on OCT and 50% of the patients required intravitreal treatment at the end of the seventh year [114]. Persistence of active disease may be related to the natural course of the disease, or due to tachyphylaxis to treatment. Tachyphylaxis refers to a diminished response to a certain medication after repeated administrations, and it has been reported in several trials in patients receiving repeated ranibizumab and bevacizumab injections [115, 116]. In such cases, use of other treatment agents is considered.

Patients who fail to respond to anti-VEGF therapy have been designated as nonresponders. There is a range of definitions for nonresponders from morphologic classifications, where nonresponders continue to have persistent subretinal or intraretinal fluid on OCT while under treatment, to functional classifications, where nonresponders have stable BCVA or a worsening of BCVA while under treatment. It has been found that switching nonresponders from ranibizumab or bevacizumab to aflibercept can result in improvements in mean central macular thickness and increase in the time interval between intravitreal injections. However, despite the anatomical improvements reported, functional improvements are rare [117, 118]. The functional and anatomical improvements from switching between ranibizumab and bevacizumab are debatable [119–121]. In addition, it can take as long as a year to notice improvement in vision, so switching early may not be advisable.

(d) *New Strategies*

More recently, the Port Delivery System (PDS) with ranibizumab from Genentech has been developed as a novel device developed to provide extended drug delivery for anti-VEGF agents. The PDS is a permanent, reusable drug reservoir that is surgically implanted through a 3.5-mm scleral incision at the pars plana. There is

a semipermeable membrane that allows continuous passive diffusion of the drug from the reservoir with higher concentration into the vitreous. The device can be refilled in the office with a specialized refill needle. The Long-Acting Delivery of Ranibizumab (LADDER) trial [122] was a phase 2 multicenter trial that enrolled 220 patients randomized in a 3:3:3:2 ratio to PDS with 10, 40, and 100 mg/mL formulations of ranibizumab, or an intravitreal injection of 0.5 mg ranibizumab monthly [123]. The primary endpoint of the study was the time to first required PDS refill. The median time to first refill in the 10 mg/mL arm was 8.7 months; in the 40 mg/mL arm, 13.0 months; and in the 100 mg/mL arm, 15.0 months. At 9 months, the reductions in central retinal thickness measurements and improvements in visual acuity were similar between the PDS 100 mg/mL group and the monthly intravitreal ranibizumab group. Vitreous hemorrhage rate postoperatively was 4.5%.

The potential for longer-term delivery of anti-VEGF and anticomplement therapy through gene therapy platforms is currently being developed [124]. Early phase studies evaluating anti-VEGF agents delivered via adeno-associated viral (AAV) vectors have demonstrated reductions in the need for intravitreal injections.

12.6 Conclusion

In the last two decades, the assessment and management of patients with AMD have dramatically improved. As described in this chapter, this was primarily due to two groundbreaking advances: the development and clinical approval of antiangiogenic injections for the treatment of neovascular AMD; and the continuous and remarkable improvements in the available imaging modalities. Currently, we have treatment strategies that effectively improve vision of patients with CNV; and the ability to visualize retinal and choroidal structures non-invasively and to a near-histological detail, thus recognizing a wide range of AMD phenotypes, which seem to have distinct prognostic implications.

Despite recent advances, limited interventions have shown to slow progression from the early to the advanced forms of AMD, and there are currently no effective treatment options available for patients with geographic atrophy. This is at least partly related to the complex, multifactorial nature of AMD, where multiple mechanisms and pathways are implicated [125]. A better understanding of the pathophysiology of this condition, including the interplay among genetic and environmental risk factors, is required to successfully halt disease progression and effectively treat the atrophic forms of AMD. Therapies reversing neurodegeneration are promising, but it is likely that future strategies will need to address multiple targets to succeed.

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