Imaging Biomarkers and Their Impact on Therapeutic Decision-Making in the Management of Neovascular Age-Related Macular Degeneration

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Neovascular age-related macular degeneration · Biomarkers · Fluid · Intraretinal · Subretinal

Abstract
These recommendations, produced by a group of Canadian retina experts, have been developed to assist both retina specialists and general ophthalmologists in the management of vision-threatening neovascular age-related macular degeneration (nAMD). The recommendations are based on published evidence as well as collective experience and expertise in routine clinical practice. We provide an update on practice principles for optimal patient care, focusing on identified imaging biomarkers, in particular retinal fluid, as well as current and emerging therapeutic approaches. Algorithms for delivering high-quality care and improving long-term patient outcomes are provided, with an emphasis on timely and appropriate treatment to preserve and maintain vision. In the context of nAMD, increasing macular fluid or leakage on fluorescein angiography (FA) may indicate disease activity regardless of its location. Early elimination of intraretinal fluid (IRF) is of particular relevance as it is a prognostic indicator of worse visual outcomes. Robust referral pathways for second opinion and peer-to-peer consultations must be in place for cases not responding to intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy.

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Introduction

Neovascular age-related macular degeneration (nAMD) is characterized by the development of choroidal neovascular membranes. This growth of abnormal blood vessels causes an accumulation of fluid and blood in the intraretinal and subretinal spaces, which can have a detrimental impact on visual acuity (VA) if left untreated [1]. Over the past decade, intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has been established as the standard of care for the treatment of nAMD by controlling the exudative process and improving visual outcomes.

The landmark MARINA and ANCHOR studies involving fixed monthly injections of ranibizumab set a high standard for VA results in nAMD treatment [2, 3]. Subsequently, other molecules (aflibercept and brolucizumab) [4, 5] and treatment approaches [6–11] have been designed, in an attempt to obtain the same favorable results, while treating with a reduced number of intravitreal injections. Treat-and-extend (T&E) [6–8] and as-needed [9–11] regimens use the presence of fluid on optical coherence tomography (OCT) as a key biomarker of nAMD activity, driving decisions regarding the need for retreatment.

This paper examines the latest evidence regarding imaging biomarkers, specifically retinal fluid, in the management of nAMD in Canadian daily practice. The objective is to provide a set of easy-to-follow guidelines (Table 1) and algorithms that will streamline the management of nAMD and optimize visual outcomes.

Methodology

The development of these expert recommendations began with a systematic literature review. Retina specialists were assigned a specific imaging- or treatment-related topic. These topics were further discussed during a meeting in Toronto, ON, Canada, on September 21, 2019. The retina specialists also reflected upon the Canadian consensus paper about the management of nAMD published in 2012 [12].

Identification and Classification of Neovascularization in AMD: Which Imaging Modality and When?

With advancements in imaging based on fluorescein angiography (FA) and OCT, a new classification arose that categorized lesions as type 1 (subretinal pigment epithelium [RPE]), type 2 (subretinal), type 3 (intraretinal), or mixed neovascularization [13]. Polypoidal choroidal vasculopathy (PCV) was considered to be a special form of type 1 nAMD, while occult, classic, and retinal angiomatosus proliferation (RAP) corresponded to types 1, 2, and 3, respectively [13, 14]. According to an OCT-based analysis, 53% of patients were diagnosed with type 1 choroidal neovascularization (CNV) and 47% with type 2 CNV; type 3 (RAP) was not assessed [15].

Fluorescein Angiography

Traditionally, FA has been considered the gold standard for the diagnosis of CNV. FA patterns observed in AMD patients can be classified as hypo- or hyperfluorescent (Table 2) [16]. Although classification of CNV lesions as classic and occult became obsolete with newer imaging modalities, leakage on FA still is an important diagnostic feature indicating an active disease process.

Indocyanine Green Angiography

Indocyanine green angiography (ICGA) provides high-quality images of the choroidal circulation and can reveal occult CNV that may be undetectable on FA [17]. With a longer operating wavelength (795–805 nm peak fluorescence emission), ICGA has the advantage of superior fluorescence through pigment, fluid, lipid, and hemorrhage than fluorescein dye, allowing deeper imaging into the retina [18]. Although ICGA is not widely used or available in Canada due to limited access to the dye and/or high costs [19], this imaging modality may be especially helpful to detect PCV, reevaluate nonresponding patients, and for conditions such as central serous choriretinopathy which may require a different therapeutic approach from that used in nAMD.

CNV appears on ICGA as a plaque, a focal hot spot, or a combination of both. Plaques (61% of cases) [20, 21] are usually formed by late-staining vessels, often correspond to occult CNV, and have a poor visual prognosis. The focal “hot spots” (approx. 30% of cases; Fig. 1) have a better prognosis and are potentially treatable by ICGA-guided laser photocoagulation [22].

FA and ICGA are invasive techniques that require intravenous dye injection, which can result in hepatic, renal, and allergic complications [23]. The incidence of adverse reactions is 0.05% for ICG and 5% for fluorescein [24]; however, FA is routinely performed in patients with advanced diabetic retinopathy, many of whom have diabetes-related renal compromise. Cases of hypotensive shock and death have been reported [25].
Imaging Biomarkers in nAMD

Fluorescein angiography
Comprehensive evaluation of a patient with suspected nAMD should include FA. However, due to considerations regarding reimbursement and other social factors, a combination of clinical examination, SD-OCT, and fundus photography is usually sufficient to diagnose nAMD with associated leakage. As a part of multimodal imaging modalities, FA has significant relevance in the management of nAMD, especially at time of diagnosis. Baseline FA may also be a useful benchmark reference for future treatment assessments (i.e., whether and how a patient is responding to therapy). Reassessment of FA may be helpful in the following situations:
- an increase in macular fluid is seen on OCT during anti-VEGF treatment in a patient whose disease has been stable/controlled
- in the presence of new hemorrhage
- in situations when vision decreases without other clinical signs
- in the presence of intraocular inflammation, retinal vasculitis, or retinal vascular occlusion
The new technologies, including OCT-A, are faster and less invasive but should continue to be used in conjunction with FA. In the era of SD-OCT, the utility of FA has diminished.
- The usefulness and necessity of FA was underscored by the limited sensitivity and specificity for fluid associated with TD-OCT; TD-OCT should therefore always be used in combination with FA.

Indocyanine green angiography
PCV is a clinical diagnosis that is optimally confirmed with ICGA. ICGA is crucial to most accurately define the location of all polyps (OCT-A is also proving valuable in this context). ICGA may also be helpful in patients with PCV who are to be treated with anti-VEGF in combination with PDT. In Canadian clinical practice, however, clinicians often forego ICGA for practical reasons (limited access to dye or equipment), and use clinical assessment and other imaging modalities to guide PDT.

Spectral-domain optical coherence tomography
In current clinical practice, SD-OCT is the new standard of care for the diagnosis and management of nAMD and the main driver for treatment decisions. It is particularly useful for determining and monitoring the fluid compartments of the retina. OCT should be performed initially and then every time a decision is to be made about whether a treatment is needed or not (pro re nata), or regarding the time interval between treatments (T&E). Once a treatment interval has been established, OCT should be used to monitor for recurrent disease activity at predetermined intervals.

Optical coherence tomography angiography
OCT-A is an emerging imaging modality, that, with time and improvements in image acquisition, may become the standard of care. Currently, it is not essential for the effective management of patients with nAMD; however, it can be a useful tool for physicians who make retreatment decisions in complex cases (i.e., patients not responding to anti-VEGF, recurrence of fluid in stable/controlled patients, etc.) without the use of an angiogram. OCT-A may become very useful in classifying nAMD into type 1, 2, or 3 (RAP), as clinical experience with this modality evolves.
- For those who already use angiography to inform their treatment decisions, OCT-A can be a useful complementary technique that provides additional information.

Fundus autofluorescence
In isolation, FAF is not useful for screening, diagnosing, or monitoring nAMD, but it complements other imaging modalities.
- FAF may be useful in detecting subclinical disease, which is of relevance when monitoring the fellow eye for signs of AMD.
- It is also of particular value for monitoring the presence and progression of GA and identifying RPE tears.
- Sensitivity and specificity of FAF, compared to other modalities, have yet to be determined.

Multimodal imaging
Comprehensive evaluation of patients with nAMD should include multimodal imaging. One modality is often insufficient for thorough investigation, which should include staging of the disease to ascertain prognosis and subsequent decision-making. However, with ongoing improvements in technologies and the quality of obtained images, in the majority of cases, adequate information can be obtained using SD-OCT with clinical examination and/or color fundus photography.
- SD-OCT is an indispensable tool to evaluate, treat, and monitor nAMD.
- After the loading phase, if there is no change from baseline in fluid after a minimum of 2 consecutive follow-up visits in patients treated with anti-VEGF, other imaging modalities should be considered to assess the underlying cause.

Fluid and its impact on therapeutic decisions
An increase in fluid is a sign of disease activity and should be treated regardless of its location.
- Foveal IRF is a negative predictor of VA outcomes and needs to be treated early and aggressively
- Patients with foveal SRF usually respond well to anti-VEGF therapy. These patients may be good candidates for the T&E approach
- Sustained drying of the retina (defined as ≥2 consecutive fluid-free visits) is an indicator of better disease control and may be associated with improved long-term outcomes.
- Fluid fluctuations in CST during anti-VEGF therapy are associated with worse visual outcomes and have a negative prognostic value; patients may require further reevaluation and consultations.

CST, central subfield thickness; FA, fluorescein angiography; FAF, fundus autofluorescence; GA, geographic atrophy; ICGA, indocyanine green angiography; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; OCT-A, OCT angiography; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; RAP, retinal angiomatous proliferation; RPE, retinal pigment epithelium; SD, spectral domain; TD, time domain; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.
Spectral-Domain OCT

Over the past decade, spectral-domain (SD)-OCT has been adopted as the gold standard for the diagnosis, follow-up, and management of nAMD CNV. It is a noninvasive, highly reproducible, high-resolution imaging tool that allows for easy visualization of anatomic changes that can be associated with angiographic leakage [26, 27].

Improvements in acquisition speed and image analysis make SD-OCT vital in decision-making for the diagnosis and treatment of nAMD. With active nAMD, SD-OCT can be used to detect signs of activity and to establish a baseline retinal thickness, volume, and fluid involvement. Additionally, SD-OCT is helpful in identifying the location and level of CNV (intraretinal, subretinal, and sub-RPE) and other lesion components (blood, fluid, pigment, and fibrosis) [28, 29]. Detection of shallow, irregular RPE elevation ([SIRE] comprising RPE increases with a greatest transverse linear dimension ≥1,000 µm, an irregular RPE layer, a height that is primarily <100 µm, and a nonhomogeneous internal reflectivity) was found to be characteristic of the “double layer sign” on SD-OCT in the presence of nonexudative macular neovascularization (NE-MNV) [30]. The authors recommended that SIRE be used as a screening tool for NE-MNV on routine OCT. SD-OCT is also valuable for the early detection of type 3 MNV before it reaches the exudative stage [31].

Three-dimensional SD-OCT volume scans are interpolated from parallel 2-dimensional OCT scans (B-scans) [32]. Current OCT devices allow for adjustment of the density of these B-scans by changing the interscan distance (ISD). Higher B-scan density results in a higher transverse resolution of the generated volume scan but also in a prolonged acquisition time, time for electronic data transfer, and the time for data reviewing. A recent study demonstrated that ISD of 60, 120, or 240 µm did not make a significant difference in the detection of treatment-relevant exudative retinal changes during monitoring of the response to intravitreal therapy of macular diseases [33]. SD-OCT can also be useful for discerning foveal morphologic changes that precede CNV formation [34]. These include new RPE or new photoreceptor defects, drusen touching the photoreceptor layer and the external limiting membrane, new drusen, and hyperreflective spots that probably represent new growing vessels.

En face swept-source (SS)-OCT is a promising rapid, noninvasive, high-resolution technology [35]. There is a correlation between angiography and en face SS-OCT images in nAMD. However, SS-OCT is not currently considered a standard requirement for nAMD monitoring.

OCT Angiography

OCT angiography (OCT-A) is a noninvasive technique for imaging the microvasculature of the retina and the choroid, potentially eliminating the need for intravascular dyes [36]. The same area is repeatedly scanned and differences are analyzed between scans over time. This allows the detection of zones containing high flow rates (i.e., changes between scans) and zones with slower or no flow at all [37]. While OCT-A offers great potential, there remains a need for a better understanding of the range of

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Table 2. Causes of hypofluorescence and hyperfluorescence

<table>
<thead>
<tr>
<th>Causes of hypofluorescence</th>
<th>Causes of hyperfluorescence</th>
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<tbody>
<tr>
<td>Blocked</td>
<td>Transmitted fluorescence</td>
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<tr>
<td>Intraretinal or subretinal hemorrhage/exudate</td>
<td>RPE atrophy</td>
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<tr>
<td>Sub-RPE hemorrhage</td>
<td>RPE rip</td>
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<tr>
<td>Pigment proliferation</td>
<td>Hard, basal laminar drusen</td>
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<tr>
<td>Pigment epithelial clumping (RPE rip)</td>
<td>Extravascular fluorescence</td>
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<tr>
<td>Vascular filling defect</td>
<td>Serous pigment epithelial detachment</td>
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<tr>
<td>Choroidal vascular atrophy</td>
<td>Soft drusen</td>
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<tr>
<td>Retinal capillary occlusion</td>
<td>Disciform scar</td>
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<td></td>
<td>Loculated fluid</td>
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<td></td>
<td>Cystoid macular edema</td>
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Abnormal vessels

| Choroidal neovascularization |
| Retinal angiomatous proliferation |

Data are from [16] with the authors’ permission. RPE, retinal pigment epithelium.
Fig. 1. FA versus ICGA. **a** Retinal angiomatous proliferation. **b** Polypoidal choroidal vasculopathy. White arrows indicate a hot spot; black arrows indicate polyps. Images courtesy of A.S. and D.T.W. FA, fluorescein angiography; ICGA, indocyanine green angiography.
technologies and methods to interpret the images [38]. As clinical trials have been designed without OCT-A-based end points, caution is required when making treatment decisions based on OCT-A imaging alone.

OCT-A is not without limitations, including artifacts that may affect the images [39, 40]. For example, the automatic segmentation of vascular layers may be challenging in eyes with myopia, even in the absence of chorioretinal complications. Projection artifacts may affect the visualization of the deeper vascular layers. Shadowing artifacts occur when the OCT beam is weakened or blocked, thereby hindering its passage to the deeper layers of the retina. OCT-A is also limited in the visualization of the larger choroidal vessels, typically displayed as silhouettes, with complete loss of signal at greater depths [41]. OCT-A also does not show leakage that can be seen in intravenous FA studies.

Up to 95% agreement has been demonstrated between different CNV patterns identified on OCT-A and treatment decisions based on conventional multimodal imaging [42]. OCT-A is particularly useful for detecting branching vessels, vascular loops, peripheral anastomosis, hypointense choriocapillaris, and subclinical CNV (Fig. 2) [43]. However, it is not as useful for detecting PCV and RAP lesions [44]. In addition, interpretation of OCT-A scans takes time, which increases the burden on the already-busy Canadian retina practice.

**Fundus Autofluorescence (FAF)**

FAF is a rapid, noninvasive retinal imaging modality that provides a density map of lipofuscin, the predominant ocular fluorophore, in the RPE [45]. FAF is especially helpful for monitoring the progression of atrophy in nAMD cases. In early non-nAMD, FAF may show widespread hyper- and hypoautofluorescent areas. Drusen have variable appearance on FAF depending on their size and composition and the health of the overlying RPE. High-risk drusenoid pigment epithelial detachments (PEDs) appear as foci of hyperautofluorescence bordered by a hypoautofluorescent halo [46]. Reticular pseudodrusen appear as elongated foci of hypoautofluorescence bound by interspersed hyperautofluorescence [47]. Reticular pseudodrusen are associated with a high risk of progression to advanced disease, including CNV and/or geographic atrophy [48].
Table 3. Imaging modalities for nAMD

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Recommendations regarding utility</th>
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<tbody>
<tr>
<td>FA</td>
<td>– At baseline prior to starting an invasive therapy (the benchmark for the assessment of future disease activity)</td>
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<tr>
<td></td>
<td>– Follow-up assessments in situations where SD-OCT does not provide sufficient information about disease activity&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>– Necessary with TD-OCT and in conjunction with SD-OCT in atypical AMD presentation</td>
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<tr>
<td>ICGA</td>
<td>– May be helpful in patients with PCV when they are to be treated with PDT</td>
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<td></td>
<td>– Reduced use in Canada due to the low availability of ICG dye</td>
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<tr>
<td>SD-OCT</td>
<td>– New standard of care for diagnosis and monitoring</td>
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<tr>
<td></td>
<td>– Should be performed frequently especially if it is used to guide treatment intervals</td>
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<tr>
<td></td>
<td>– Particularly useful for diagnosing type 3 CNV and monitoring retinal fluid</td>
</tr>
<tr>
<td>OCT-A</td>
<td>– Allows for identification of subclinical features (membranes) not seen by other modalities&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>– Useful for detecting serous PED, branching vessels, vascular loops, peripheral anastomosis, hypointense choriocapillaris</td>
</tr>
<tr>
<td></td>
<td>– Not as useful for detecting PCV or leakage</td>
</tr>
<tr>
<td></td>
<td>– Unnecessary for standard of care</td>
</tr>
<tr>
<td>FAF&lt;sup&gt;d&lt;/sup&gt;</td>
<td>– Helpful in identifying drusen and non-nAMD</td>
</tr>
<tr>
<td></td>
<td>– The most useful for tracking geographic atrophy (i.e., when patients with stable vision on anti-VEGF treatment start noticing changes)</td>
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<tr>
<td></td>
<td>– Helpful for detecting PED</td>
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<td></td>
<td>– Hyperautofluorescence at the borders of active CNV may indicate viable and proliferating RPE</td>
</tr>
<tr>
<td></td>
<td>– Increasing AF with treatment is a good prognostic sign</td>
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<tr>
<td></td>
<td>– Loss of AF is highly predictive of loss of vision</td>
</tr>
</tbody>
</table>

AF, autofluorescence; AMD, age-related macular degeneration; CNV, choroidal neovascularization; FA, fluorescein angiography; FAF, fundus autofluorescence; ICGA, indocyanine green angiography; OCT, optical coherence tomography; OCT-A, OCT angiography; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; SD, spectral domain; TD, time domain; VEGF, vascular endothelial growth factor.

<sup>a</sup> Recommendations are based on the Canadian landscape.

<sup>b</sup> Continuous presence of fluid despite treatment, new hemorrhage, unexplained decrease in vision, increase in disease activity in patients previously well-controlled, RPE tear, etc.

<sup>c</sup> Clinical significance has yet to be confirmed (i.e., frequency of treatment, benefits of earlier intervention, etc.).

<sup>d</sup> Intensity may change with circadian rhythms, adaptation to the dark, and photoreceptor “bleaching.”
In the early stage of nAMD, FAF usually appears normal because the activity of RPE cells remains preserved [45]. Classic and occult type 1 neovascularization usually appears hypoautofluorescent due to the blockage or atrophy of the overlying RPE. However, CNV may be bordered by hyperautofluorescence due to RPE proliferation or photoreceptor loss [49]. Hemorrhages and exudates are initially hypoautofluorescent due to excitation light absorption, but may become hyperautofluorescent after undergoing organization [45]. PED can present as a cartwheel-like configuration with increased and decreased levels of signal intensity (Fig. 3). RPE tears are readily shown with FAF.

Limitations of FAF include low signal strength and autofluorescence artifacts from the anterior segment. Software to analyze and quantify hypo- or hyperautofluorescence intensity has been developed but is not readily available. FAF intensity may change with circadian rhythms (autofluorescence decreases at the end of the day), adaptation to the dark, and photoreceptor “bleaching.”

A multimodal imaging approach is required for the diagnosis of different subtypes of neovascularization. Recommendations for the use of various imaging modalities in the management of nAMD in Canada are provided in Table 3 and a diagnostic algorithm is shown in Figure 4. For follow-up assessment and monitoring, it is recommended one continues with the imaging modality that was used for the initial diagnosis, so as to appropriately assess and record changes. In the case of atypical presentation(s) or unusual findings, ancillary modalities can be used to determine the course of the disease.

**Imaging Biomarkers and Their Prognostic Value in nAMD**

Over the past decade, several imaging biomarkers appeared to have predictive and prognostic value in the management of nAMD. Further research into a definitive association between prognostic markers such as subretinal hyperreflective material, atrophy, fibrosis, and predictive outcomes is required.

**Retinal Thickness**

The measurement of retinal thickness is the easiest method to quantify retinal changes on OCT [48]. Continued increase in retinal thickening indicates leakage in the area. Integrated automated software algorithms are capable of segmenting the internal limiting membrane and the RPE or Bruch’s membrane as the inner and outer retinal boundaries. The average thickness in a circular field (1 mm in diameter) centered on the fovea is used as a quantitative outcome measure in clinical trials and to assess treatment response in clinical practice. The main limitation of retinal thickness as a biomarker is that it includes an array of retinal compartments, and the simple measurement of central retinal thickness does not differentiate the contribution of these components to pathological changes and visual outcomes [50].

**Intraretinal Fluid**

On OCT, intraretinal fluid (IRF) appears as diffuse retinal thickening (i.e., ≥ 100 µm increase in retinal thickening indicates fluid) or as hyperreflective cystoid spaces, depending on the imaging quality. IRF usually indicates
that the neovascular network has breached from its confined sub-RPE space and has started to infiltrate the neurosensory retina. Thus, IRF is a sign of a more aggressive lesion type or a sign of late presentation in chronic occult CNV. In treatment-naïve nAMD patients, the rate of IRF findings at the initial presentation ranges from 52 to 76% [51–53]. IRF at presentation may predict a delayed response to treatment and has been associated with a poorer prognosis [50].

One should differentiate between cystoid fluid secondary to exudative CNV (“exudative intraretinal cyst” [IRC]) and that associated with neurosensory degeneration (“degenerative IRC”). While exudative IRCs are relatively large ovoid spaces overlying PED (type 1 or 3 lesions) or neovascular tissue (type 2 CNV), degenerative IRCs are generally small, square, sharply demarcated, hyporeflective spaces over dysfunctional RPE [50, 54]. Lai et al. [54] differentiated degenerative from exudative IRCs if they had 2 of the following 3 morphological criteria: alteration of the underlying RPE layer, a square-shaped lesion with >1 concave or straight border, and small size of the IRC (greatest dimension <125 μm) without obvious expansion of adjacent layered retinal structure. Degenerative IRCs are not a sign of active disease and do not respond to anti-VEGF treatment, with resultant poor visual improvement up to 12 months after treatment initiation [54–56].

**Subretinal Fluid**

Subretinal fluid (SRF) is associated with all lesion types and is typically the first exudative sign in type 1 lesions [51]. It is the only biomarker that is consistently associated with a positive response to anti-VEGF treatment. In addition, eyes with baseline SRF are less likely to develop macular atrophy even when undergoing an intensive monthly anti-VEGF regimen [57, 58]. Although patients with baseline SRF derive larger VA benefits from antiangiogenic treatment than those without SRF, one should keep in mind that recurrence of SRF is a sign of disease activity and, if left untreated, may have a negative impact on visual outcomes [59, 60]. On the other hand, in the FLUID study, tolerance of some SRF (<200 μm; relaxed arm) did not adversely affect visual outcomes; however, the presence of IRF in a higher proportion of patients in the relaxed treatment group at month 24 suggests that SRF may lead to IRF over time [61].

**Sub-RPE Fluid**

Studies suggest that changes in the sub-RPE spaces potentially reflect the primary disease activity in serous and vascularized PED [57, 62], with the sub-RPE space a predictor of recurrence after the loading phase with anti-VEGF [63]. This indicates that the changes in the sub-RPE space could be a sensitive marker to monitor disease activity. A recent clinical trial identified sub-RPE fluid in 43% of subjects [5]. Spatial correlation for PED was found to be higher for cystoid IRF than for SRF [64].

**Pigment Epithelial Detachment**

Traditionally, clinicians have not included PED in the decision algorithms for treatment indications, and none of the large-scale prospective treatment trials have included it in their retreatment criteria. Recent studies revealed that PED-associated neovascular reactivations may be implicated in long-term vision loss in patients treated with individualized anti-VEGF regimens [50]. A larger PED is also an important risk factor for the development of RPE tears, a severe complication in nAMD with often poor functional outcomes [65]. A dome-shaped PED is associated with lower central macular thickness at presentation, but it does not appear to affect the response to treatment [66].

**Central Subfield Thickness**

Fluctuations in central subfield thickness (CST) during anti-VEGF therapy are associated with worse visual outcomes and a negative prognostic value [67]. Pooled analysis of the Comparison of the AMD Treatment Trials (CATT) and Inhibit VEGF in Age-Related Choroidal Neovascularisation (IVAN) trial demonstrated that CST fluctuation after the loading phase is associated with poor visual outcomes [68]. Although the amplitude of VA gain is individual, data from these 2 analyses indicate that a more stable CST reflects better disease control and the associated better visual outcomes [67, 68].

**Fluid and Its Impact on Therapeutic Decisions**

A 5-year follow-up of the CATT demonstrated that 60% of the eyes studied had IRF, 38% had SRF, and 36% had sub-RPE fluid [69], potentially due to undertreatment. Considering the evidence demonstrating the impact of fluid on long-term visual outcome, the management of fluid presents a significant unmet medical need. Any increase in fluid seen on OCT may indicate disease activity and should be further evaluated, and, if confirmed to be associated with neovascularization, treated regardless of its location.
Confirmed nAMD

Determine and record morphology (presence / location of fluid, PVD, PED, etc.)

Initiate treatment with monthly anti-VEGF loading dose (as per indication)

Treat as per indication until maximum response is achieved

Maximum response

• Complete resolution of fluid (SRF, IRF, and sub-RPE) without new retinal hemorrhage
  OR
• No further reduction of fluid for at least 2 consecutive visits, as seen on OCT, if VA is improved, and in the absence of new retinal hemorrhage

BASELINE

Signs of disease activity at baseline or anytime during treatment

• Fluid
• New hemorrhage
• Loss of vision (>5 letters or clinically relevant VA loss)

Criteria for treatment suspension can be assessed at any time point

Criteria for treatment suspension

• Extended period of disease quiescence
• Eyes with advanced fibrovascular scarring, geographic atrophy, or degenerative cysts

Primary criteria for extension

• No fluid on OCT or stabilization of fluid on OCT
• No new hemorrhage

Supporting criteria for extension

• No further flattening of serous or vascularized PEDs and no further visual impairment

Extension of treatment interval

• No fluid on OCT AND
  • Loss <5 letters
  • Increase <100 μm CRT
  • No new neovascularization
  • No new macular hemorrhage

Maintenance of treatment interval

• No fluid on OCT AND
  • Loss <5 letters
  • Increase <100 μm CRT
  • No new neovascularization
  • No new macular hemorrhage

Shortening of treatment interval

• New fluid on OCT AND
  • Fluid ≥ baseline on OCT
  • Loss ≥5 letters
  • Increase ≥100 μm CRT
  • New neovascularization
  • New macular hemorrhage

Revert back to original loading dose

Major deterioration (large recurrence or increase of fluid on OCT associated with visual loss of >5 letters or presence of a subfoveal or large extrafoveal hemorrhage)

If continuous increase in disease activity despite shortening the interval, consider further investigations to determine potential underlying reasons or switch to another anti-VEGF

Consider further investigations to determine potential underlying reasons. If deemed appropriate decrease interval or switch to another anti-VEGF

YES

NO

Maximum response achieved?

(For legend see next page.)
As foveal SRF responds well to anti-VEGF treatment, patients with SRF should be monitored closely and treated accordingly. SRF in nAMD seems to positively influence not only visual function but also the need for retreatment. In a post hoc analysis comparing the outcomes of fixed frequent and infrequent anti-VEGF treatments, eyes with SRF had similarly favorable VA outcomes regardless of the treatment regimen [61, 70]. Current data suggest that eyes with SRF at presentation are likely to exhibit a disease course that can be managed with anti-VEGF injections with extended intervals up to every 12 weeks. Eyes with SRF may be the ideal candidates for T&E regimens; however, these patients still require close monitoring and appropriate management of retinal fluid. Evidence that SRF indicates a good prognostic VA outcome should be interpreted with caution, as any fluid seen on OCT may indicate disease activity, and the end goal should always be a dry retina. Current guidelines recommend retreatment with anti-VEGF in the presence of disease activity, defined as IRF, SRF, or sub-RPE fluid or hemorrhage, lesion growth, or visual deterioration [71–73]. Furthermore, the volume of SRF appears to be an independent predictor of response [74]. Patients with greater baseline SRF thickness require more injections than patients with SRF <118 μm. Sustained retinal drying (defined as ≥2 consecutive fluid-free visits) is an indicator of better disease control and may be associated with improved long-term outcomes. Figure 5 depicts a fluid-based treatment algorithm for nAMD. Although FA is the gold standard for diagnosis of CNV in clinical trials, access to this modality in real-world clinical practice is becoming increasingly difficult; OCT-based criteria have therefore been adopted.

**Management of PCV and RAP**

Left untreated, symptomatic PCV may lead to severe vision loss, so active intervention is strongly indicated [19]. Current treatment options for PCV include anti-VEGF and verteporfin photodynamic therapy (PDT). While patients with branching vascular networks usually respond to anti-VEGF therapy, those with solitary polyps tend to be anti-VEGF-resistant and responsive to PDT, used alone or as an adjunct to anti-VEGF therapy [75]. Anti-VEGF agents improve visual function by restoring normal retinal thickness and reducing the reuptake of VEGF after PDT, while PDT facilitates polyp regression. The efficacy of these treatments as monotherapy versus combination therapy was evaluated in the EVEREST trial [76], which demonstrated that verteporfin PDT, either alone or combined with ranibizumab 0.5 mg, was superior to ranibizumab monotherapy in achieving complete regression of polyps in patients with symptomatic macular PCV. In the Afibercept in Polypoidal Choroidal Vasculopathy (PLANET) trial [77], afibercept monotherapy was associated with improved visual and/or functional outcome in >85% of the PCV patients. The benefit of adding PDT could not be determined due to the low number of patients who met the criteria to receive it.

Patients with RAP usually respond well to anti-VEGF therapy with or without PDT [78–80]. Other approaches include laser photocoagulation of feeder vessels, or intra-vitreal triamcinolone to reduce exudation (intraretinal/subretinal), followed 7–14 days later by PDT [81].

**Therapeutic Options and Goals in 2021 and Beyond**

The treatment goal for nAMD is to achieve the best possible VA benefits through early initiation of therapy, which is then maintained through continuous timely disease monitoring and retreatment. A proactive treatment approach, where assessment and retreatment occur during the same visit, minimizes the need for additional visits and alleviates the burden on the treating clinicians and patients.

When applied according to the approved dosing, treatment extension allows for injection intervals to be increased gradually in a stepwise fashion to maintain stable visual and anatomic outcomes [7, 8, 82]. Extension may be considered for eyes without macular fluid on OCT and stable vision. The main criteria for shortening treatment intervals are persistent macular fluid with stable vision, recurrent fluid, decrease in vision in the presence of fluid,
new macular hemorrhage, new CNV, or any other sign(s) of exudative disease activity considered vision-threaten-
ing in the opinion of the treating clinician [8].

Currently, 3 anti-VEGF therapies are available glob-
ally, 2 of which (ranibizumab and aflibercept) are ap-
proved for intravitreal use. Bevacizumab, an anti-VEGF
agent indicated for the treatment of some forms of cancer,
is reconstituted and used off-label to treat nAMD. The
use of these agents in clinical practice has further im-
proved the understanding about the disease, its natural
history, and the need for individualized treatment. Afli-
bercept’s every-8-week (q8w) dosing schedule for the
treatment of wet AMD (following 3 monthly loading dos-
es) offered a promise of longer interval between treat-
ments; however, some patients were found to require
more frequent doses to maintain their VA gains. The
“sawtooth” pattern in retinal thickness observed in the
VIEW trials after the loading doses hinted at the neces-
sity for a shorter dosing schedule [83]. Thus, the search
continues for a therapeutic approach that will lead to a
sustainability of VA gains and a reduced number of visits/ 
treatments.

Brolucizumab has recently been approved for the
treatment of patients with nAMD in some countries. This
single-chain anti-VEGF antibody fragment binds to all
isoforms of VEGF-A and blocks their action [84]. The
smaller molecular size of brolucizumab (28 kDa, vs. 48
kDa for ranibizumab and 115 kDa for aflibercept) allows
for the delivery of a higher molar dose than is possible
with larger molecules, thereby offering the potential of
more effective tissue penetration [85]. This superior pen-
etration is believed to confer better fluid control across all
layers of the retina, resulting in similar visual outcomes
and better anatomical outcomes. The phase 3 HAWK and
HARRIER trials compared brolucizumab (3 and 6 mg
given as 3 monthly loading doses at 0, 4, and 8 weeks,
and then every 8 or 12 weeks depending on disease activity)
to aflibercept (2 mg q8w) [5]. At 48 weeks, noninferiority
of BCVA compared to aflibercept (the primary outcome)
was achieved with both 3- and 6-mg doses. Brolucizumab
was also significantly superior in achieving a dry macula,
with more reduction in IRF, SRF, and sub-RPE fluid at
weeks 16, 36, and 48. Early postmarketing reports of vas-
culitis, including retinal occlusive vasculitis, were con-
firmed by an external safety review committee as a rare
(15.47/10,000 injections) safety signal [86, 87].

Promising approaches in advanced phases of clinical
development include a bispecific monoclonal antibody
(faricimab) and a port delivery system (PDS) with ranibi-
zumab.

Faricimab is the first bsipic antibody designed for
intravitreal use to simultaneously neutralize both angi-
opoietin-2 (Ang-2) and VEGF-A with high potency and
specificity [88]. In nAMD, Ang-2 works synergistically
with VEGF to drive a decrease in the abnormal blood ves-
sel growth and fluid leakage which contribute to vision
loss. Ang-2 also plays an important role in multiple as-
pects of inflammation in nAMD [89, 90]. Topline results
from the phase 3 TENAYA and LUCERNE studies
showed that faricimab at fixed intervals of up to every 16
weeks achieved noninferior VA outcomes to those for
aflibercept every 8 weeks [91].

The PDS with ranibizumab, a small, refillable eye im-
plant (approx. 3 mm in length) was designed to allow pa-
ients with nAMD to avoid retreatment for several
months. The device is placed through a 3.5-mm scleral
incision in the pars plana. Topline results from the phase
3 Archway study found that 98.4% of PDS patients were
able to achieve ≥6 months without additional treatment
and had visual outcomes comparable to those who re-
ceived monthly intravitreal ranibizumab [92]. An open-
label extension to the PORTAL study was initiated in Sep-
tember 2018 and is ongoing [93].

Conclusions

nAMD is a chronic, life-long condition requiring on-
going treatment with regular follow-up and monitoring
to control exudative disease activity. The frequency of fol-
low-ups can pose a significant burden for patients, clini-
cians, and the healthcare system. To reduce this burden,
many clinicians currently rely on imaging biomarkers,
particularly the presence of retinal fluid, to adjust treat-
ment frequency according to disease activity. Although
recent evidence indicates that the location of fluid carries
a prognostic value with regard to the response to treat-
ment and visual outcomes, it is important to keep in mind
that the presence of any fluid may indicate disease activ-
ity and needs to be appropriately treated. Sustained dry-
ning of the retina is an indicator of better disease control
and may be associated with improved long-term out-
comes. Thus, clinicians should opt for treatments with
the ability to improve dry retina and are then less likely to
require shortening of the treatment interval. The ultimate
treatment goal for nAMD in 2021 and beyond should be
the maintenance of good VA with less frequent visits/in-
jections for all patients.
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