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Anti-VEGF Treatment and Optical Coherence Tomography Biomarkers in Wet Age-Related Macular Degeneration

Maja Vinković, Andrijana Kopic and Tvrтка Benašić

Abstract

Age-related macular degeneration (AMD) is one of the most common causes of severe visual loss in middle and old-age population, and often leads to serious deterioration in quality of life. Currently, the first-line treatment for neovascular AMD (nAMD) are intravitreal injections of anti-vascular endothelial growth factor (VEGF) medications, including bevacizumab, ranibizumab, and aflibercept and also latest commercially available drug, brolucizumab. During initial examination and imaging and treatment follow-up for patients with nAMD, optical coherence tomography (OCT) is used to predict and assess the therapeutic response and guide the treatment. Several OCT-based biomarkers, including the central subfoveal thickness (CSFT), the presence of intraretinal cysts (IRCs) or subretinal fluid (SRF), and the presence of pigment epithelial detachment (PED), were found to influence baseline visual acuity or visual improvements. Recent analyses of large randomized control trials (RCTs) summarized the usefulness of these OCT-based biomarkers. However, many of these early studies relied on time-domain OCT to evaluate the retinal structures thus providing less precise evaluation of the retinal details. After introduction of spectral-domain OCT (SD-OCT) which provided high resolution images, recent studies offered new insights in specific morphological changes and their different impact on visual function in nAMD. For example, these advancement in resolution offered new classification of IRCs into degenerative and exudative which impacts treatment strategy and final outcome in the treatment of nAMD. Moreover, the recent data disclose a substantial difference between RCTs and real-world studies regarding the response to anti-VEGF therapy. In conclusions, IRCs and PED are associated with poor visual improvement in nAMD in a realworld setting. Both IRCs and SRF responded better than PED to anti-VEGF therapy. These observations mandate large longitudinal studies focusing on the usefulness of these high resolution SD-OCT biomarkers in real-world situations.

Keywords: Anti-VEGF treatment, biomarkers, intraretinal cysts, intraretinal fluid, neovascular AMD, OCT, pigment epithelial detachment, subretinal fluid

1. Introduction

Improving or maintaining visual acuity is the main target of treatment of neovascular age-related macular degeneration (nAMD). Standard nAMD care mandate frequent intravitreal (IVT) antivascular endothelial growth factor (VEGF) injections, which represents a heavy burden on patients, health systems, and physicians.

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries, with a global prevalence of 8.69% [1]. The prevalence of AMD increases with age among all ethnicities and in all geographic regions, as a result of a growing aging population [2].

Age-related macular degeneration is a progressive, chronic, multifactorial disease of the retina that can lead to visual impairment and blindness, mostly affecting individuals aged more than 60 years [3]. The disease progresses from early to advanced stages and can be divided into 2 major advanced forms: neovascular (wet) AMD (nAMD) and geographic atrophy in dry AMD [4]. A smaller proportion of patients with AMD (20%) are diagnosed with nAMD, but it is responsible for the majority (90%) of vision loss cases and presents as acute painless loss of vision [5, 6]. Neovascular AMD is characterized by the presence of choroidal neovascularization (CNV), a pathologic form of angiogenesis resulting in leakage of fluid that accumulates in the retina, subretinally or below the retinal pigment epithelium (RPE); other features include the development of RPE tears, hard exudates, hemorrhage, or fibrous disciform scar tissue formation [7–9].

These clinical abnormalities in patients with nAMD lead to a gradual loss of retinal photoreceptors, resulting in decreased vision and even blindness if disease progression is not prevented [10].

Central vision is the key to various daily activities, including a person's ability to read, drive, and recognize faces [11]. The loss of central vision that accompanies AMD greatly affects an individual's quality of life [12].

Deleterious effect of vision loss on an individual's quality of life mandates further development of effective treatment modalities and new molecules to treat nAMD.

2. Advances in nAMD treatment

Preservation of visual function is the main goal for nAMD treatment. This is achieved by inhibition of the new blood vessel growth and reduction of the fluid leakage [13]. Vascular endothelial growth factor is a major molecule which contributes to development of CNV [14]. Choroidal neovascularization can be slowed by inhibiting VEGF binding to its receptor, VEGF receptor-2, on blood vessels, which is the major proangiogenic pathway [15]. Anti-VEGF agents are antibodies which neutralize VEGF binding to its receptor and they have different mechanisms of action. They reduce fluid leakage from the CNV, stop growth, and lead to regression of CNV [16]. The introduction of the anti-VEGF drugs into clinical practice has immensely improved the prognosis for patients with nAMD, in such a way that nAMD is no longer considered an incurable disease [17]. The first anti-VEGF agent approved in 2004 by Food and Drug Administration (FDA) was pegaptanib sodium, an aptamer that binds VEGF₁₆₅ [18]. Ranibizumab, an antibody fragment that binds all VEGF-A isoforms was FDA approved in 2006 after the ANCHOR and MARINA studies [19, 20]. In the following years, from 2006 till 2013, there were 2 other anti-VEGF therapies available for nAMD treatment: aflibercept and conbercept, approved based on the results of the VIEW 1 and VIEW 2 studies, and PHOENIX study, respectively [21, 22]. Both of them are antibody fusion proteins [23].

Two other anti-VEGF agents approved for therapy in oncology are used “off-label” for nAMD: ziv-aflibercept and bevacizumab [7]. Current care standards for nAMD include regular intravitreal (IVT) injections of anti-VEGF therapy [24]. This poses a substantial burden on patients, as well as health systems worldwide [3]. For some patients, anti-VEGF treatment involves monthly injections over a long period of time, making patient adherence and monitoring difficult, which in turn has consequences for visual and anatomic outcomes [25]. Also, the cost associated with managing nAMD is substantial [26]. In an attempt to lessen the load of frequent therapy and costs associated with anti-VEGF medications, some clinicians proposed alternative dosing strategies which are different from those in the registered clinical trials (q4- or q8-weeks). These include pro re nata (PRN) and treat-and-extend (TAE) regimens [27]. They attempt to provide the same efficacy and at the same time more convenient regimen that is easier to adhere to and is taking into account individual OCT features of the patient.

Brolucizumab, a newly developed anti-VEGF drug for nAMD treatment, has demonstrated longer durability and improvement in visual and anatomic outcomes in clinical studies in a q12-week regimen, indicating its potential to reduce treatment burden as an important therapeutic tool in nAMD management [28].

3. The role of OCT + OCT-A in nAMD

3.1 Specific OCT biomarkers

Several OCT-based biomarkers, including the central subfoveal thickness (CSFT), the presence of intraretinal cysts (IRCs) or fluid (IRF), subretinal fluid (SRF), and sub-RPE fluid or pigment epithelial detachment (PED), were found to be associated with baseline visual acuity and response to the anti-VEGF treatment (**Figure 1**). One of the main goals in the management of nAMD has been the removal of fluid in the macular compartments [26]. The clinical significance of fluid depends on its location where it plays a major role in determining the long term success of the treatment and its presence should be recorded at baseline, according to the guidelines from the Vision Academy. Fluid segments should be assessed individually and fluid status evaluated after loading phase and throughout the course of treatment [29, 30].

The introduction of OCT into everyday clinical practice allowed a new classification of CNV according to its location, complementing fluorescein angiography (FA) and indocyanin green angiography (ICGA) [31]. In OCT, type 1 CNV, located between Bruch membrane (BM) and RPE, corresponds to PED, often accompanied

Figure 1.
OCT biomarkers.

by subretinal fluid and in later stages of disease by IRC [32]. Type 2 CNV presents as subretinal hyperreflective material (SHRM) and shows concomitant IRF and SRF [33]. SHRM may be composed of exudative fluid, fibrin, blood, or scarring and its characteristics may change during treatment period [34]. According to CATT study, SHRM was present in 77% of treatment-naïve eyes at baseline with the prevalence decreasing to 58% at week 4 after treatment and further to 46% after 2 years [35]. It is hypothesized to be caused probably by a dehydration and condensation of the active CNV component [36, 37].

IRC overlying PED, accompanied by SRF, are typical features commonly present in retinal angiomatous proliferation (RAP), classified as type 3 CNV by Freund et al. [38]. Mature type 3 lesions, associated with serous PEDs, are highly responsive to anti-VEGF therapy [39]. However, the development of GA has frequently been described in association with treatment of RAP lesions [40].

3.1.1 Central subfoveal thickness

The greatest importance of CSFT was actually in the research because it was used as a criterion for continued treatment in trials of various drugs and treatment protocols. If the reduction in CSFT after injection is less than 25%, this is considered a criterion for reinjection [41, 42].

Value of CSFT depends mostly on the amount of retinal fluid in the different retinal compartments, so in most cases a higher CSFT is also a sign of a worse VA. If the cause of CSFT is mostly retinal fluid, it will be reduced by treatment with anti-VEGF factors, and VA in this case will be better or not get worse. Recently there was an observation that there is a direct correlation between vision, fluid, the amount of fluid, and fluctuations in CST [28]. A new option is to look at what effect a drug has on fluctuations in CST, which may prove to be extremely important in identifying patients at risk for closer monitoring and more aggressive therapy.

The presence of an epiretinal membrane (ERM) and the accumulation of drusenoid or fibrous material may also be responsible for a higher CSFT. In this case, the prognosis for CSFT reduction with anti-VEGF treatment is usually poor [28, 41].

A certain percentage of subjects in clinical trials as well as patients in clinical practice developed geographic atrophy (GA) after treatment with anti-VEGF factors. Risk factors for such development include the presence of foveal fluid and monthly dosing of injections. In the CATT study, approximately 38% of subjects developed GA after 5 years, mainly those receiving ranibizumab rather than aflibercept. In the case of GA development, a lower CSFT will also mean a significantly lower VA [7, 43].

3.1.2 Intraretinal fluid

Intraretinal fluid appears as round or oval hyporeflective spaces – cysts, but may also present as diffuse thickening of the neurosensory retina [1]. Intraretinal cysts (IRCs) are OCT biomarkers for various retinal diseases such as nAMD, diabetic macular edema, central retinal vein occlusion, and uveitic macular edema.

Since IRCs often differ in their shape and size, and also in their response to anti-VEGF therapy, some authors have divided them into exudative and degenerative. The criteria taken into account were the size of the cyst, its shape, and the possible alteration of the continuity of the RPE below the cyst. Degenerative cysts were described as smaller than 125 μm , usually square in shape and with RPE alterations below the cyst itself, while exudative cysts are more often ovoid and larger [41, 44, 45]. Intraretinal fluid usually results from active fluid exudation, but the

degenerative cysts may originate from passive fluid accumulation due to atrophy of neurosensory elements [1]. Exudative cysts had better initial response to 3 loading monthly injections of anti-VEGF treatment whereas degenerative cysts had lower response to the therapy, persisted for a longer time and were associated with lower VA after treatment [44–47].

3.1.3 Subretinal fluid

Subretinal fluid can be characterized as hyporeflective fluid accumulation overlying the RPE layer. It resolves in most eyes in response to anti-VEGF treatment, however, not as rapidly as IRF.

According to the several studies, the presence of SRF at baseline or after 1-year treatment did not significantly affect VA [44, 48, 49]. Residual SRF may not always represent ongoing neovascular activity. It may instead be dysfunction of the RPE leading to SRF accumulation, much like central serous chorioretinopathy [50, 51]. Among patients treated with a PRN regimen, those who presented with SRF achieved even higher VA gains [52]. VA was stable regardless of treatment frequency [53]. The pathomechanism for the beneficial role of SRF has not been fully explained but possible explanations suggest the preservation of photoreceptor integrity, less IRF, RPE atrophy and fibrosis [54].

3.1.4 Pigment epithelial detachment

Pigment epithelial detachment (PED) (**Figure 2**) the anatomical separation of the RPE from the Bruch membrane i.e. sub-RPE fluid is present in about 30–80% of nAMD patients based on the CATT, EXCITE, and VIEW studies [41, 55, 56].

PED lesions have been classified based on clinical findings, angiography and OCT assessment (height, width, greatest linear diameter, area, volume, reflectivity, progression and response to treatment of PED lesions) [57]. Three subtypes of PED may be identified based on the reflectivity of the material under the RPE: serous (primarily hyporeflective; hollow), solid (primarily hyperreflective; drusenoid), and mixed (combination of solid and serous PEDs; fibrovascular) [58–60]. The CNV membrane itself corresponds to hyperreflective material along the back surface of the PED, readily visible by enhanced-depth imaging, or a tomographic notch within the PED, identifiable by conventional OCT [61].

PED has a negative effect on VA only in combination with additional components, mostly IRF [47, 62]. In VIEW studies, the baseline presence of PED, disrupted external limiting membrane (ELM) and ellipsoid zone (EZ), and greater CSFT were associated with poor baseline VA [46]. However there are some controversial data by real-world study where initial VA was worse and visual improvement

Figure 2.
Pigment epithelial detachment.

poorer if PED was present before treatment regardless of IRC or SRF presence [44]. Microperimetry analysis has shown higher retinal sensitivity for SRF and serous PED (sPED) than for IRF and fibrovascular PED (fvPED) [63]. The volume of fvPED at baseline was associated with impaired VA and PED growth seemed to precede fluid recurrence [64–66].

When SRF is located on the top of a PED (rather than on its edge), without associated IRF, hemorrhage, then probably the PED is not vascularized and will response poorly to anti-VEGF therapy [67]. PEDs are also less responsive to anti-VEGF treatment than SRF or IRC in nAMD [41, 46]. Serous PEDs showed better response to IVIs than fibrovascular ones which may suggest that they are possible signs of lesion activity. Serous PEDs showed most improvement in VA whereas fvPEDs showed most reduction in PED height, especially with aflibercept [50, 57, 68–70]. Fibrovascular PEDs may be difficult to treat, but even these eyes can gain vision with anti-VEGF therapy. The IVIs change PED morphology in such way that their content becomes more hyperreflective, suggesting an increasing fibrovascular maturization of the CNV [71]. PEDs behavior and functional outcomes are influenced by the treatment regimen. VIEW trials found that the switch from a monthly to an as-needed regimen led to reactivation of PED with a resultant decline in visual outcome, especially in patients who developed secondary IRC following that change [46]. The recurrence of PED is the primary event of neovascular activation [47].

Treatment should focus on vision gains rather than PED resolution because there is no apparent correlation between anatomical and functional improvement in most eyes with PED and nAMD. More frequent anti-VEGF doses may improve anatomical response, without correlation with vision improvement [29]. Atrophy may complicate eyes with PED and nAMD after anti-VEGF therapy, especially in association with complete PED resolution [29].

In 15–20% of eyes with PEDs a RPE tear that may lead to decline or loss of vision spontaneously but also as a serious complication of anti-VEGF therapy. Hyperreflective lines in near-infrared (NIR) images and PEDs greater than 500 μm to 600 μm in height on OCT present an indicator of an increased risk in developing an RPE tear in eyes where the sub-RPE CNV has created contractile folds in response to the treatment [72, 73]. RPE tears after anti-VEGF therapy only developed in patients with serous PED (14.6%) [74].

In conclusion, the presence or persistence of a PED may still be compatible with relatively good visual acuity, but may require more regular treatment.

3.2 Specific OCT-A biomarkers

Noninvasive OCT angiography (OCT-A) generates images of the retinal and choroidal vessels, with the excellent sensibility and specificity for detection of the CNV compared to FA and ICGA [75, 76]. OCT-A provides detailed visualization of the CNV complex in patients with nAMD and its evolution in response to anti-VEGF treatment, disclose a perfused vascular network in nonexudative stage of CNV and also in advanced cases of evident nAMD with fibrotic scars and history of prior treatment with anti-VEGF therapies [77]. CNV type 1 and 2 seem to be more easily visualised on OCT-A compared with retinal angiomatous proliferation (RAP) or polypoidal lesions [78].

Current studies evaluate the association between OCT-A parameters, structural OCT changes and functional response on anti-VEGF therapies. Five qualitative criteria have been recognized on OCT-A: (1) Numerous branching capillaries between major vessels separating the lesion area into fractals, (2) end-to-end anastomoses or intervascular anastomoses within the lesion, (3) arcades or vascular loops at the vessel termini, (4) major, well-defined filamentous vessels, and (5) peri- or

intralesional nonvascularized hypointense halos surrounding or embedding the CNV membrane [75]. Greater rate of small branching vessels and peripheral arcades have been detected in immature lesions and a dead-tree appearance in hypermature lesions [79]. A qualitative classification algorithm has been developed based on neovascular density as a predictive factor for clinical activity [80]. Recently, some authors have demonstrated quantitative biomarkers for nAMD disease activity: (1) CNV's blood flow surface area (SA), (2) vessel density (VD), (3) fractal dimension (FD), and (4) lacunarity index (LAC) [81].

Blood flow SA is a readily available and well-studied OCT-A parameter. Previous qualitative assessments of OCT-A images in CNV networks showed that most of the lesions demonstrated shrinkage of fine peripheral vessels and arteriogenesis of the remaining vessels after anti-VEGF treatment [82]. The branching complexity and blood flow area decrease after the loading doses then regrow and return to the original size at 12 months irrespective of the treatment protocol. The same modifications of blood flow area in patients followed under PRN and TAE regimens [83]. SA also seems to have a weak association with functional outcomes (i.e. VA), highlighting the need to assess other parameters. Finally, the baseline blood flow area had an inverse association with the number of IVIs concerning baseline FD [83].

FD quantifies branching pattern complexity and organization of the vascular structure. It varies according to the number of secondary divisions of the CNV: the higher the number of discernible secondary divisions, the higher the FD value [84]. Many authors demonstrated attenuation and pruning of secondary ramifications after anti-VEGF treatments, with subsequent decrease of the FD value. A FD values is lower in the inactive stage than in the active stage [83, 84]. A weak association between blood flow aspect (FD) and retinal fluid suggests that factors other than CNV morphology are responsible for retinal exudation [79]. There is a poor association between the most studied quantitative OCT-A parameters and functional outcomes at 12 months' follow-up. FD did not differ between good and bad responders [83].

Lacunarity (LAC) is a measure of the size of gaps within a structure. Higher values reflect heterogenic texture of vascular networks and lower values reflect a more homogeneity of vascular skeleton. The results showed that arrangement of lacunas of the vascular plexus do not change after anti-VEGF, therefore lacunarity may be an OCT-A parameter for nAMD follow-up [85].

According to some investigators, patients with a lower baseline FD and a lower SA have higher odds of having 8 or more IVI injection during the first year. Typical examples of patients that required less than 8 IVI in the first year of treatment are large and complex CNVs. On the other hand, typical examples of patients that required more than eight IVI in the first year of treatments are small lesions with a disorganized architecture [83]. A hypothesis is that in the presence of high VEGF levels, CNVs would have numerous tiny branches and a disorganized architecture, reflecting an aggressive angiogenic process with greater exudation and a heavier treatment burden. In eyes with lower VEGF availability, CNV would grow without leakage maturing their branching architecture toward a complicated network before exudation becomes overly symptomatic [86]. In conclusion, it seems that all evaluated OCT-A parameters were poor biomarkers in predicting anatomic and functional response but baseline FD and SA were the best biomarkers regarding treatment burden.

4. The role of visual acuity on long term prognosis

Early response to anti-VEGF therapy has been shown to be an important predictor of VA recovery in nAMD treatment. VA after 3 months of consecutive intravitreal injections is a better prognostic factor than baseline VA [87]. Likewise,

early morphological change of the described OCT biomarkers is a very important prognostic factor for overall treatment outcome.

Thus, early accurate monitoring of treatment responses by analysis of OCT findings and VA is of great importance to optimize the number of injections during treatment in achieving the goal of vision function recovery.

5. Conclusions

Introduction of OCT into everyday clinical practice has revolutionized diagnosis and management of nAMD. This diagnostic tool has pivotal role in terms of disease monitoring and evaluation of treatment efficacy. Many studies give hope that in the future we will be able to offer a better or possibly individual approach to the anti-VEGF treatment that will give the optimal morphological recovery of the macula and VA. The risk factors identified for persistent CNV activity may help clinicians to identify patients for closer monitoring and more aggressive therapy.

The main OCT features predictive of persistent disease activity are IRCs, SRF, sPED recurrence, and those indicative of poorer VA outcome are IRCs, large extent of SHRM damage to the photoreceptor or RPE layer [35]. Exudative IRCs have been shown to require monthly treatment, in particular after recurrence of PED [37, 88]. Patients with IRC after 12 monthly IVIs have shown a higher risk for fibrosis and RPE atrophy compared with patients presenting refractory SRF [89]. By contrast, SRF is associated with stable VA, regardless of treatment frequency, and with better visual gain [50, 51, 90, 91]. Consequently, SRF is an ideal feature for identifying patients suitable for flexible or treat and extend regimens.

By contrast, SRF is associated with stable VA, regardless of treatment frequency, and with better visual gain, and consequently, is an ideal for flexible or treat and extend regimens [50, 51, 90, 91]. In conclusion, these subtypes tell us what outcomes we are hoping to achieve. We can personalize the treatment to some extent – treatment intervals can be maintained or extended where disease inactivity is achieved, i.e. IRF is improving or SRF is stable, or more aggressive or in shortened intervals in patients with new and/or increased fluid. It is postulated that persistent IRF should never be tolerated whereas with persistent SRF we are less likely to treat until dry [92]. Advisably is also identifying patients with fluctuations in CSFT, who are convenient for closer monitoring and more aggressive therapy [28].

OCT-A may differentiate active CNV lesions from stable fibrous complexes which could be relevant for treatment decisions. Quantitative OCT-A parameters have shown as poor biomarkers in predicting anatomic and functional response although blood flow area and FD are slightly better than the others.

Recently, automated quantification algorithms have been proposed for the analysis of OCT images with CNV, namely multi-resolution graph-theoretic-based surface detection for PED segmentation and machine learning-based pixel classification for IRC and SRF segmentations [93]. Machine learning algorithms are particularly suitable for determining treatment effect after the loading phase [94]. Computational analysis of OCT images is expected to become even more widespread in the clinical treatment strategies. This will hopefully establish a set of standardized protocols that will allow personalized anti-VEGF treatments based on identifying important differences in retinal responses between patients.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

VEGF	vascular endothelial growth factor
AMD	age-related macular degeneration
nAMD	neovascular age-related macular degeneration
OCT	optical coherence tomography
CSFT	central subfoveal thickness
IRC	intraretinal cysts
SRF	subretinal fluid
PED	pigment epithelial detachment
sPED	serous
fvPED	fibrovascular
ELM	external limiting membrane
EZ	ellipsoid zone
RCT	randomized control trials
SD-OCT	spectral domain optical coherence tomography
IVT	intravitreal
IVI	intravitreal injection
CNV	choroidal neovascularization
RPE	retinal pigment epithelium
PRN	pro re nata (as needed)
TAE	treat-and-extend
ERM	epiretinal membrane
GA	geographic atrophy
RAP	retinal angiomatous proliferation
SHRM	subretinal hyperreflective material
NIR	near-infrared
OCT-A	optical coherence tomography angiography
SA	surface area
VD	vessel density
FD	fractal dimension
LAC	lacunarity index
FAZ	foveal avascular zone
FA	fluorescein angiography
IVGA	indocyanin green angiography
BM	Bruch membrane

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