



A paradigm shift in imaging biomarkers in neovascular age-related macular degeneration

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ABSTRACT

Neovascular age-related macular degeneration (AMD) has undergone substantial break-throughs in diagnostic as well as therapeutic respect, with optical coherence tomography (OCT) allowing to identify disease morphology in great detail, and intravitreal anti-vascular endothelial growth factor therapy providing unprecedented benefit. However, these two paths have yet not been combined in an optimal way, real-world outcomes are inferior to expectations, and disease management is largely inefficient in the real-world setting. This dilemma can be solved by identification of valid biomarkers relevant for visual function, disease activity and prognosis, which can provide solid guidance for therapeutic management on an individual level as well as on the population base.

Qualitative and quantitative morphological features obtained by advanced OCT provide novel insight into exudative and degenerative stages of neovascular AMD. However, conclusions from structure/function correlations evolve differently from previous paradigms. While central retinal thickness was used as biomarker for guiding retreatment management in clinical trials and practice, fluid localization in different compartments offers superior prognostic value: Intraretinal cystoid fluid has a negative impact on visual acuity and is considered as degenerative when persisting through the initial therapeutic interval. Subretinal fluid is associated with superior visual benefit and a lower rate of progression towards geographic atrophy. Detachment of the retinal pigment epithelium was identified as most pathognomonic biomarker, often irresponsive to therapy and responsible for visual decline during a pro-re-nata regimen. Alterations of neurosensory tissue are usually associated with irreversible loss of functional elements and a negative prognosis. Novel OCT technologies offer crucial insight into corresponding changes at the level of the photoreceptor – retinal pigment epithelial – choriocapillary unit, identifying the biological limits of therapeutic interventions.

To optimally benefit from high-resolution multi-modal imaging, an integrated analysis of all functional and structural features is required involving reliable automated algorithms and computational data analyses. Using innovative analysis methods, retinal biomarkers can be used to provide efficient personalized therapy for the individual patient, predictive disease- and population-based models for large-scale management and identifying promising targets for the development of novel therapeutic strategies.

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1. Introduction

The advent of intravitreal therapy using vascular endothelial growth factor (VEGF) inhibition has introduced a new standard of care in the treatment of patients with neovascular age-related macular degeneration (AMD) (Brown et al., 2006; Rosenfeld et al., 2006). While AMD-associated choroidal neovascularization (CNV) has previously almost inevitably led to extensive structural damage and irreversible functional loss up to legal blindness, modern therapy ideally allows for substantial recovery with long-term stabilization of visual acuity in the majority of patients (Lim et al., 2012b). The significant progress in retinal therapy has even dethroned neovascular AMD as the leading cause of legal blindness in developed countries (Campbell et al., 2012). However, the enormous costs and efforts of sustained anti-VEGF therapy in one of the leading diseases in the developed world place a tremendous burden on patients and healthcare givers (Hawkes, 2012). Moreover, real-life outcomes deviate drastically from the level of benefit suggested by pivotal clinical trials, with little improvement despite huge investment in treatment and monitoring (Holz et al., 2015); so much so that in neovascular AMD, the burden of disease has turned into a burden of care (Schmidt-Erfurth et al., 2015).

The major challenge associated with anti-VEGF treatment in neovascular AMD is the profound heterogeneity in individual patient profiles. While some individuals may do well with a low number of injections over time, even the most intensive monthly therapy may not provide the desired disease control in other patients. Moreover, recurrence of neovascular activity following previous disease stabilization often occurs in an unpredictable fashion (Funk et al., 2009), with recurrent neurosensory damage invariably leading to irreversible loss of visual function (Gerding et al., 2011). There is a critical unmet medical need to identify, characterize, and

validate biomarkers that could provide solid guidance for an efficient individualized treatment with regards to optimal functional outcome and disease management. Such biomarkers would enable the treating physician to tailor personalized treatment to each patient's individual disease and need, in order to provide adequate disease control, minimize recurrence and neurosensory damage, and limit the number of invasive and costly interventions. Moreover, reliable biomarkers allowing prediction of disease progression may help to eventually reduce the substantial monitoring burden.

The aim of this article is to provide a comprehensive review of the current knowledge in the field of biomarkers relevant in the management of neovascular AMD. The different types of biomarkers described in the scientific literature range from clinical data such as patient age or visual acuity over the individual genetic background, to a wealth of morphologic parameters obtained from *in-vivo* retinal imaging. Of these candidate biomarkers, morphological information based on optical coherence tomography (OCT), the most important diagnostic modality in AMD, shows the most consistent and promising potential as clinically applicable biomarkers. Table 1 summarizes individual biomarkers and their reported effect on visual function and treatment outcomes and highlights the complexity of prognostic evaluation.

2. Method of literature research

We conducted a comprehensive review of the literature on biomarkers and prognostic factors in neovascular AMD. The PubMed database was searched to identify relevant peer-reviewed articles published until March 2015. The keywords for the search included, but were not limited to: *Neovascular (wet) age-related macular degeneration* or *age-related maculopathy* in context with biomarker(s), predictive factor(s), optical coherence tomography,

Table 1

Summary of biomarkers in neovascular age-related macular degeneration.

Biomarker	Prognostic value	Magnitude of effect	Comment
Pharmacogenetics (CFH, HTRA1, ARMS2, VEGFA genes)	Poorer VA gains if high-risk alleles present	5–10 letters	Data contradictory
Patient age	Poorer VA gains in older patients	5 letters less gain for each additional 14–19 years of age	
Baseline visual acuity	Poorer VA gains with better baseline VA Better final VA in eyes with better baseline VA	0.65 letters less gain for each additional letter of better VA at baseline (centred on 52 letters)	Interaction effect with baseline retinal morphology
Lesion type	Larger VA gains in RAP lesions	3 letters	
Haemorrhage >50% of lesion	Poorer VA at baseline, similar VA gains	5 letters	
Lesion size	Poorer VA gains in larger lesions	4–10 letters	
Retinal thickness	Poorer VA if retinal thickness below or above the normal range	Weak correlation	Correlation lost during therapy
Intraretinal cystoid fluid (exudative)	Poorer VA if present at baseline Poorer VA gains if present at baseline	10 letters 5 letters	
Intraretinal cystoid fluid (degenerative)	Horizontal extension correlates with VA levels	Strong correlation (60%)	
Subretinal fluid	Poorer VA if present at week 12 Better initial VA if present at baseline Larger VA gains if present at baseline	15 letters 5 letters 5 letters	
External limiting membrane and photoreceptor loss	Associated with lower retreatment needs	Up to 40 letters	Poor reproducibility
Hyperreflective foci	Poorer VA if signal absent	Not reported	Not prognostic of VA change
Outer retinal tubulation	Restoration of signal correlated with VA gain	10 letters	
Subretinal hyperreflective material	Poorer VA gains if present at baseline Poorer VA gains if developing over time Poorer VA if present	3 letters 5–15 letters	
Pigment epithelial detachment	Reduced contrast sensitivity if present Risk factor for sustained VA loss	5 letters	
Retinal pigment epithelial atrophy	Poorer VA gains if present at baseline		
Choroidal thickness	Risk factor for progressive VA loss during individualized dosing	15 letters	Limited data
Posterior vitreous detachment	Risk factor for sustained VA loss		
Vitreomacular adhesion	Poorer VA gains if thinner at baseline Predictive of lower retreatment needs	10 letters	
	Poorer VA gains if not treated monthly		

VA, visual acuity; RAP, retinal angiomatous proliferation.

fluorescein angiography, intraretinal fluid, subretinal fluid, pigment-epithelial detachment, geographic atrophy, outer retinal tubulation, hyperreflective foci or dots, subretinal, choroidal thickness, vitreomacular adhesion, posterior vitreous detachment, and pharmacogenetics. All abstracts were reviewed to identify articles pertinent to biomarkers in neovascular AMD. Non-peer-reviewed articles were excluded.

3. Clinical definition of age-related macular degeneration

Age-related macular degeneration is defined clinically by fundus examination. Two widely adopted classification schemes require the presence of drusen and/or pigmentary changes (including hyperpigmentation or pigment epithelial atrophy) for clinical diagnosis (Ferris et al., 2005, 2013). Such grading schemes have also been shown to provide a clinically useful risk assessment that may surpass even the precision of genetic testing (Ferris et al., 2013; Stone, 2015).

The onset of neovascular AMD may be subtle and evident to neither patient nor physician. On clinical examination, the first signs of choroidal neovascularization include haemorrhage, intraretinal or subretinal fluid, or a tortuous perifoveal blood vessel in retinal angiomatous proliferation. The patient may be symptomatic with metamorphopsia, reduced visual acuity, or a central scotoma. Presence of any of these symptoms or signs initiates the typical sequence of diagnostic events, which most importantly includes OCT, and potentially additional more invasive diagnostic procedures such as fluorescein and indocyanine green angiography. Most therapeutic trials defined active, subfoveal leakage on fluorescein angiography as a major inclusion criterion.

Unfortunately, the majority of patients with neovascular AMD present at a late stage of disease. Thus adequate risk stratification and (home-) monitoring strategies are required to enable an earlier detection and therapy of neovascular AMD in the future (Chew et al., 2014). Furthermore, the disease stage of the fellow eye is a major risk factor and should be considered for monitoring strategies (Ferris et al., 2013).

4. Current therapeutic concepts in neovascular AMD

The landmark trials in anti-VEGF therapy of neovascular AMD mandated a fixed monthly dosing protocol throughout the entire 96-week follow-up period and thus established the gold standard in antiangiogenic dosing regimens (Brown et al., 2006; Rosenfeld et al., 2006). However, fixed monthly therapy does not only represent overtreatment for the vast majority of patients, it also maximizes potential safety risks. These risks include infectious endophthalmitis (Fileta et al., 2014), retinal detachment (Meyer et al., 2011), persistent intraocular pressure rise (Singh and Kim, 2012), development of geographic atrophy (Grunwald et al., 2014a) and systemic side effects (Modi et al., 2015).

Nevertheless, in terms of visual acuity benefits, investigators consider fixed monthly dosing as a guarantee for maximum efficacy (Schmidt-Erfurth et al., 2014a). The feasibility of a less frequent, individualized dosing regimen based on imaging parameters (pro re nata, PRN) was first suggested by encouraging results in the Prospective Optical Coherence Tomography Imaging of Patients with Neovascular Age-Related Macular Degeneration Treated with intraOcular Ranibizumab (PrONTO) study (Fung et al., 2007; Lalwani et al., 2009). However, the excellent treatment outcomes

obtained in PrONTO were not replicated in large-scale prospective trials, and less frequent dosing regimens generally provided inferior functional outcomes (Chakravarthy et al., 2013; Holz et al., 2011; Regillo et al., 2008; Schmidt-Erfurth et al., 2011). Real-world outcomes of PRN dosing are even inferior to clinical trial results (Cohen et al., 2013; Tufail et al., 2014).

The emerging concept of a treat-and-extend regimen may provide better disease control in some neovascular AMD patients than PRN therapy. However, individual extension lengths are difficult to determine *a priori*, and even infrequent disease recurrences may have adverse functional consequences at a lifetime scale (Abedi et al., 2014; Berg et al., 2015; Gupta et al., 2010; Rayess et al., 2015). A head-to-head comparison of treat-and-extend versus monthly therapy has not been published to-date.

In the scientific literature, two main reasons can be identified for the failure of PRN dosing in clinical practice. First, OCT-based monitoring is usually applied in a less rigorous manner than in a clinical trial setting suggesting monitoring every four weeks. There is clear evidence from several studies that less frequent monitoring is associated with poorer functional outcomes. Data from these studies are summarized in Table 2.

Second and most importantly, there is an apparent lack of sensitive and robust biomarkers for the management of OCT-based retreatment. Even a most rigorous “no tolerance” PRN approach, as used in the comparison of age-related macular degeneration treatments trial (CATT), failed to achieve equivalent outcomes to monthly therapy (Martin et al., 2012). Thus, treatment must clearly be administered before the development of irreversible changes in the neurosensory retina, at least in patients for whom recurring fluid is detrimental to visual function. Imaging biomarkers, which may guide such individualized retreatment decisions, are currently being controversially discussed as a result of ongoing intensive research efforts.

5. Biomarkers unrelated to OCT imaging

The main focus of this review article is on biomarkers for the management of anti-VEGF treatment obtained by high-resolution imaging of the posterior fundus, and is discussed in Section 6. However, several other biomarkers unrelated to OCT imaging — serological, genetic, clinical, or biomarkers based on other imaging

methods — are also critically important to the understanding of OCT-based biomarkers. Non-ocular biomarkers may be less relevant in therapeutic management, but include relevant risk factors for the development of late AMD. These non-OCT biomarkers are discussed in the following paragraphs.

5.1. Serological and genetic biomarkers

5.1.1. Pharmacogenetics

Progress in genetic research, in particular genome-wide association studies (GWAS) among large populations, have led to the discovery of several single-nucleotide polymorphisms (SNPs) in multiple genes that are associated with various stages of AMD. The most important mutations include the Y402H variant within the complement factor H (CFH) gene on chromosome 1q31, the A69S variant within the age-related maculopathy susceptibility 2 (ARMS2) gene on chromosome 10q26, and a promoter sequence alteration of the high-temperature requirement factor A1 (HTRA1) gene on chromosome 10q26, plus a large number of additional mutations (Deangelis et al., 2011). Moreover, mutations in vascular endothelial growth factor A (VEGFA) and vascular endothelial growth factor receptor 2 (VEGFR2) genes have been implicated in the pathomechanism of CNV in neovascular AMD (Deangelis et al., 2011).

The pharmacogenetic relevance of these SNPs on treatment response in neovascular AMD has been investigated in multiple studies with contradictory evidence (Dedania et al., 2015; Finger et al., 2014). Concerning the mean change in best-corrected visual acuity (BCVA) score during the course of anti-VEGF treatment, some studies report a 5–10-letter difference between patients with low- and high-risk alleles in the CFH, HTRA1, ARMS2 and VEGFA genes (Abedi et al., 2013a, 2013b; Smailhodzic et al., 2012). However, other reports failed to replicate these findings (Hagstrom et al., 2013, 2014; Park et al., 2014). A rigorous analysis of the large-scale alternative treatments to inhibit VEGF in age-related macular degeneration (IVAN) trials did not find associations between genotype and anatomic response as determined by central retinal thickness (Lotery et al., 2013).

Clinical implications

In summary, the reported pharmacogenetic associations in neovascular AMD treatment are unrevealing. The available

Table 2
Comparison of monitoring frequencies in studies using flexible-dosing antiangiogenic therapy for neovascular age-related macular degeneration.
Overall, studies employing a fixed 4-weekly monitoring interval show larger mean visual acuity benefits than studies using a less intensive monitoring scheme.

	Number of patients	Mean visual acuity change at 12 months (letters)
Studies using 4-weekly monitoring		
Fung et al. (2007)	40	9.3
Holz et al. (2011)	513	3.6
Gerdin et al. (2011)	104	5.0
Mekjavić et al. (2011)	149	6.0
Martin et al. (2011)	298	6.8
Kaiser et al. (2012)	112	8.1
Larsen et al. (2012)	133	4.4
Katz et al. (2012)	29	10.0
El-Mollayess et al. (2012)	60	11.0
Chakravarthy et al. (2012)	284	5.5
Mean visual acuity change		5.6
Studies using >4-weekly monitoring		
Cohen et al. (2009)	124	0.7
Leydolt et al. (2010)	102	-1.0
Bandukwala et al. (2010)	95	2.9
Arias et al. (2011)	90	7.0
Kumar et al. (2011)	81	3.1
Hjelmqvist et al. (2011)	352	1.0
Patel and Tufail (2012)	64	6.9
Bloch et al. (2013a)	279	-0.4
Mean visual acuity change		1.5

evidence to date does not explain the individual variability in treatment outcomes through pharmacogenetic mechanisms, particularly when compared to the prognostic relevance of retinal morphology. Routine genetic testing in the management of neovascular AMD is therefore currently not warranted. Further research in larger patient cohorts is required to clarify the individual genetic risks in antiangiogenic treatment.

5.1.2. Serological biomarkers

Inflammatory processes including dysregulation of the complement system undoubtedly play a major role in the pathogenesis of AMD (Charbel Issa et al., 2011). Involvement of the alternative pathway of the complement system has been shown locally in drusen as well as in the macular Bruch's membrane/choriocapillary complex by immunohistochemical studies (see extensive reviews in *Progress in Retinal and Eye Research* by Anderson et al., 2010; and Hageman et al., 2001). Systemically, increased levels of activation products of the alternative complement pathway, particularly markers of chronic complement activation (Ba and C3d), have been demonstrated in the peripheral blood of patients with AMD (Hecker et al., 2010; Reynolds et al., 2009; Scholl et al., 2008). Studies investigating the impact of complement activation levels on treatment response are lacking thus far.

Elevated plasma fibrinogen levels have been implicated as a moderately influential risk factor for the development of late AMD. Other serological biomarkers with weaker association with neovascular AMD include serum total and HDL cholesterol levels and triglyceride levels (Chakravarthy et al., 2010).

Clinical implications

The level of systemic complement activation may be a useful systemic biomarker for risk assessment in patients with AMD. Therapeutic complement inhibition has provided a promising horizon for the treatment of non-neovascular AMD (lampalizumab, www.clinicaltrials.gov/NCT01229215), and may potentially be of relevance in combined treatment approaches to neovascular AMD in the future.

5.2. Biomarkers ascertained by clinical examination

5.2.1. Non-ocular clinical biomarkers

5.2.1.1. The role of patients' age. Clearly, increasing age is a strong risk factor for the development of neovascular AMD. However, age is also a biomarker for therapeutic outcomes. Numerous studies, including subgroup analyses of the major randomized prospective trials, have consistently reported a significant association between older age and poorer outcomes of anti-VEGF therapy for neovascular AMD (Boyer et al., 2007; Kaiser et al., 2007; Lim et al., 2012a; Wickremasinghe et al., 2011; Ying et al., 2013). The correlation between patient age and visual acuity change over time during treatment appears to be fairly linear, nevertheless weak. Patients in the oldest age-group (>85 years) demonstrated on average approximately 5 early treatment diabetic retinopathy study (ETDRS) letters lower visual acuity gains after 12 months of therapy compared to patients in the youngest age group (<65 years) in the Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in AMD (ANCHOR), Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and CATT programs (Boyer et al., 2007; Kaiser et al., 2007; Ying et al., 2013). Multivariate modelling predicted 5 letters less improvement in VA score with each additional 14 years of age in MARINA (Boyer et al., 2007) and with each additional 19 years of age in ANCHOR (Kaiser et al., 2007).

Whether this finding correlates with the increased incidence of geographic atrophy in older patients, requires additional analyses.

5.2.1.2. Other systemic risk factors. Other non-ocular risk factors for AMD have been extensively discussed in a recent systematic review (Chakravarthy et al., 2010). Therefore, the current article focussing on biomarkers for therapeutic management of neovascular AMD will only provide a high-level overview. The recent meta-analysis by Chakravarthy and colleagues, including several prospective, cross-sectional and case-control studies, reported the following highly significant risk factors for the development of late AMD (in addition to increasing age): Current cigarette smoking, a family history of AMD, and previous cataract surgery, although previous cataract surgery was not confirmed in a prospective trial (Chew et al., 2009). Moderately influential clinical risk factors included a higher body mass index, a history of cardiovascular disease, and hypertension. Risk factors with weaker associations with late AMD were female gender, ethnicity (non-hispanic white), diabetes, light iris colour, and a history of cerebrovascular disease (Chakravarthy et al., 2010).

5.2.2. Ocular clinical biomarkers: baseline visual acuity

The individual level of visual acuity (VA) score at the time of treatment initialization is one of the key factors influencing visual acuity outcomes in antiangiogenic therapy. It is well established that the VA change caused by anti-VEGF treatment is influenced by a ceiling effect corresponding to baseline VA levels. Specifically, patients with a lower initial VA generally demonstrate larger VA gains than patients with a higher initial VA score, and eyes with highest initial VA levels may even experience a net loss of mean VA. MARINA and CATT suggested an almost 10-letter difference in average VA gains between patients in the highest VA group (>20/40 Snellen) compared to poorer initial VA groups (<20/100) (Boyer et al., 2007; Ying et al., 2013), although these studies did not adjust for retinal morphologic factors, which in turn strongly affects baseline VA. If balanced for retinal morphology, the effect of baseline VA is somewhat less pronounced: Multivariate analyses based on the "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD" (VIEW) trial data, including retinal morphology, demonstrated approximately 0.65 letters more VA improvement for each one letter of poorer VA score at baseline centred on 52 letters (Schmidt-Erfurth et al., 2015). Noteworthy, the impact of morphological features on functional outcomes is particularly pronounced in patients with lower initial VA levels (Schmidt-Erfurth et al., 2015). For instance, among eyes with low initial VA, those without intraretinal morphological changes had much higher VA gains than those suffering from intraretinal fluid – a pattern that was not as strong in eyes with high initial VA levels. The visual acuity level after three monthly anti-VEGF treatments was also reported to be a good predictor of final visual acuity (Bloch et al., 2013a).

With respect to the VA-based ceiling effect, it is crucial that scientific studies report, compare, and discuss absolute VA outcomes and not just VA change in treatment trials for neovascular AMD. Indeed, despite the lower VA gains (or even VA losses) in patients with higher initial VA, patients with higher initial VA scores generally also achieve higher final VA results (Tufail et al., 2014). Fig. 1 illustrates the relationship between initial VA, VA change and final VA results based on CATT, IVAN, and real-world data.

Based on known structure/function correlations, mathematical modelling may precisely determine the individualized functional potential for each patient in consideration of baseline VA and individual retinal morphology (Waldstein et al., submitted for publication-a). This would enable the evaluation of the efficacy of intravitreal therapy based on the extent to which the individual functional potential of each patient is exploited by the applied treatment. Such advanced surrogate variables for visual function may have the potential to replace mean BCVA change as an outcome variable in clinical trials of neovascular AMD treatment.

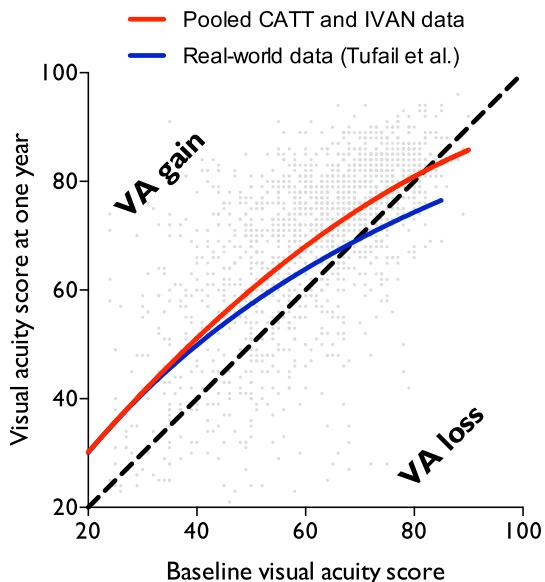


Fig. 1. Relationship between initial visual acuity, visual acuity change and final visual acuity during therapy of neovascular age-related macular degeneration (i.e., the ceiling effect). The interpolation curves illustrate final visual acuity levels dependent on baseline visual acuity in the controlled trials CATT and IVAN as well in the real-world UK neovascular AMD database study (Chakravarthy et al., 2012; Martin et al., 2011; Tufail et al., 2014). While patients with poorer initial visual acuity afford relatively larger functional gains, patients with better initial visual acuity may not gain vision at all, or even lose visual acuity during therapy. This phenomenon was particularly pronounced in the real-world scenario. Controlled clinical trials were more successful at preventing vision loss in patients with good initial visual acuity. The authors thank Dr. Maureen Maguire and Dr. Usha Chakravarthy for making the data available. Real-world data based on the data provided in Tufail et al. (2014).

Clinical implications

The main message in terms of clinical management is to treat patients as early as possible, with the aim to intervene as long as functional neurosensory structures are not irreversibly compromised. Although patients with lower visual acuity have higher chances of gaining vision, a delay in treatment with associated functional loss may not allow restoring vision to the initial levels.

5.3. Angiographic lesion characteristics

Traditionally, fluorescein angiography has been regarded as the method of choice for the diagnostic evaluation of neovascular AMD and its hallmark feature, choroidal neovascularization. However, in the era of intravitreal antiangiogenic therapy, the division of CNV lesions into the individual angiographic lesion types has considerably lost relevance.

The historical importance of angiographic characteristics as biomarkers for treatment outcomes stems from evidence provided by the macular photocoagulation studies (MPS), in which the indications for destructive and irreversible laser treatment were strictly based on lesion composition (MPS Study Group, 1984). Also in another therapeutic concept, photodynamic therapy, the differentiation between occult, classic and minimally classic lesions was critically important for treatment indication (TAP Study Group, 2001; VIP Study Group, 2001). Photodynamic therapy was based on thrombotic, i.e. mechanical occlusion of neovascular channels and therefore demonstrated different results in distinct angiographic lesion types, with best outcomes in classic CNV and inferior outcomes in purely occult lesions.

In contrast to laser-based therapies, anti-VEGF agents are not restricted to particular anatomical constellations and provide

excellent efficacy across all lesion types. The pharmacologic approach using biologics is independent of the anatomic vascular architecture as it targets vascular fenestration, permeability of vascular walls and endothelial proliferation. Moreover, modern technology has introduced a more comprehensive understanding of the nature of neovascular choroidal lesions based on advanced vascular imaging. Today, the main indications for fluorescein angiography have shifted to an initial angiographic examination at baseline to compliment OCT and consolidate the primary diagnosis, subsequent OCT-based monitoring during follow-up, and added angiography when there is a change in clinical status not explained by the OCT result (Castillo et al., 2015; Schachat and Thompson, 2015).

Most recently, extraction of vascular features from regular non-invasive OCT, referred to OCT angiography, by innovative software algorithms has emerged and will likely integrate conventional FA methods into the multimodal OCT armamentarium (Hong et al., 2014).

With reference to the traditional classification of CNV types, some studies have reported that minimally classic and classic lesions were associated with poorer VA outcomes and required more injections than occult lesions (Horster et al., 2011; Ying et al., 2013), whereas other studies did not confirm these findings (Heimes et al., 2011). RAP lesions were reported to show larger mean VA benefits from anti-VEGF treatment (Ying et al., 2013); however, RAP lesions are also associated with poorer initial VA levels, which in turn influences the average VA gain. Lesions including large amounts of haemorrhage (>50% of the total lesion size) showed on average 5 letters lower VA at baseline, but had a similar visual prognosis to patients without large haemorrhage in CATT (Altawee et al., 2015).

Several studies, including post-hoc analyses of major phase III trials, provide solid evidence for an association between angiographically determined CNV lesion size and visual acuity outcomes. In ANCHOR, which solely included eyes with predominantly classic CNV lesions, patients with the smallest lesions (≤ 1 disc area) showed approximately 10 ETDRS letters more VA gains than patients with the largest lesions (≥ 4 disc areas) (Kaiser et al., 2007). Concerning occult lesions, MARINA demonstrated similar, albeit less strong evidence (Boyer et al., 2007). The mean adjusted difference in VA gain between the largest and smallest CNV lesions was merely 4 letters in CATT (Ying et al., 2013).

In light of the addition of OCT as the diagnostic modality of choice, Freund et al. have introduced an updated classification of CNV lesions based on both OCT and angiographic features, which may provide a better practical applicability in the modern era (Freund et al., 2010). In this classification, lesions are primarily characterized as predominantly sub-pigmentepithelial (Type I), subretinal (Type II), and intraretinal (Type III). These types roughly correspond to the angiographic types of occult (Type I) CNV, classic (Type II) CNV, and retinal angiomatic proliferation (RAP, Type III). In terms of distribution, Type II lesions were found at a rate below 10%, while Type I and III lesions represented the vast majority of lesion types (Jung et al., 2014). The previously described classic CNV is now recognized to represent a tip-of-the-iceberg subretinal component of a primary type I lesion (Freund et al., 2010) not requiring specific therapeutic measures.

Type III (RAP) lesions are considered to respond favourably to therapy with a low number of retreatments needed (Hemeida et al., 2010; Querques et al., 2012). Smaller studies report an exquisite anatomical responsiveness of Type III lesions to anti-VEGF therapy (Nagiel et al., 2015). However, as Type III neovascularization is generally accompanied by intraretinal changes (Nagiel et al., 2015), early aggressive therapy is required to prevent irreversible neurosensory damage (Waldstein et al., submitted for publication-a) as described in detail in Section 6.2. Moreover, RAP lesions are intrinsically associated with a high rate of development of

geographic atrophy (GA), which has been shown to also occur spontaneously in fellow eyes of patients treated for a RAP component in the contralateral eye (Viola et al., 2005). This may limit the long-term outcome of this lesion type (Cho et al., 2015; Grunwald et al., 2014a; McBain et al., 2011).

Unfortunately, reliable data on the prognostic relevance of the different lesion types as suggested by Freund are currently lacking, particularly since large-scale treatment trials have not yet adopted the OCT-based grading scheme. The availability of non-invasive vascular imaging based on OCT technology will strengthen the evaluation of vascular features in the management of neovascular AMD and will re-introduce "angiographic" biomarkers into therapeutic considerations (Leitgeb et al., 2014). OCT angiography will allow the delineation of vascular components in a depth-resolved fashion relating to the individual changes at the retinal level (Hong et al., 2014; Miura et al., 2011), and measure vascular flow as a follow-up parameter (Jia et al., 2014).

OCT-based vascular measures obtained in conjunction with conventional cross sectional OCT may have important implications in unveiling the pathogenesis of AMD and optimizing disease management. "Tangled" mature vessels were identified underlying lesions with good maintenance of visual function over time, suggesting that the neovascular net plays a role in improving oxygen and nutrient supply in advanced disease of the retinal pigment epithelium (RPE) in AMD (Rahimy et al., 2014). The role of anti-angiogenic therapy may be to control neovascular leakage and to establish a balance between maintenance of a mature choroidal net and prevention of fibro-vascular proliferation (Rahimy et al., 2014). Advanced angiographic OCT may further reveal the initial pathogenetic steps in CNV formation highlighting choriocapillary perfusion defects preceding neovascular growth or GA development (McLeod et al., 2009; Mullins et al., 2014; Whitmore et al., 2015).

Clinical implications

Based on the available data, the prognostic relevance of fluorescein angiography in neovascular AMD seems overshadowed by structural imaging techniques such as OCT, highlighting fluid-related changes rather than vascular pathologies and leakage dynamics. As per the guidelines of the American Academy of Ophthalmology (AAO Retina/Vitreous PPP Panel, 2015), and the European Society of Retina Specialists (Schmidt-Erfurth et al., 2014a), angiography remains indicated at baseline and when there is a change in clinical status that is not explained by the OCT result. Prominent developments based on angiographic OCT and Doppler OCT may change the vascular concepts significantly in the near future.

5.4. Biomarkers associated with fundus autofluorescence

Fundus autofluorescence is capable of visualizing the naturally or pathologically occurring fluorophores in the retina, mainly lipofuscin (Delori et al., 1995). Due to its ability to delineate geographic atrophy with superior contrast than in colour fundus photography, fundus autofluorescence has been used extensively in non-neovascular AMD studies (Schmitz-Valckenberg et al., 2008), particularly as automated planimetry allows for user-friendly measurement of the geographic atrophy area. Specific qualitative patterns of hyper- and hypoautofluorescence were suggested to correlate with the growth rates of geographic atrophy, a finding not confirmed by other groups (Holz et al., 2007).

However, in neovascular AMD, the diagnostic value of fundus autofluorescence appears to be limited. As a pure en-face imaging technique, fundus autofluorescence is not able to appreciate the depth-resolved changes in the different retinal compartments, which are fundamentally important biomarkers in the diagnosis and management of neovascular AMD (Keane et al., 2012).

Moreover, the masking presence of haemorrhage, oedema, and hyperpigmentation makes the interpretation of fundus auto-fluorescence images challenging, particularly regarding the assessment of RPE cell loss. Studies assessing the evolution of GA, in a series of patients with differently treated neovascular AMD during long-term follow-up and in a dry stage of advanced disease, provided evidence for progressive RPE damage in neovascular disease as well (Kumar et al., 2013). Moreover, investigators demonstrated a 10-letter VA disadvantage after several anti-VEGF treatments in eyes with confluent hypoautofluorescence involving the fovea (Sato et al., 2015).

Clinical implications

Due to the lacking depth resolution and challenging interpretation, assessment strategies using fundus autofluorescence may eventually not be helpful in the diagnostic management of active neovascular disease. In contrast, OCT (particularly its functional extension, polarization-sensitive OCT) enables the reliable identification and measurement of pigment epithelial atrophy areas in relation to choroidal neovascularization (Ahlers et al., 2010; Schutze et al., 2015). The role of pigment-epithelial atrophy as a biomarker in neovascular AMD is discussed in Section 6.9.

6. Optical coherence tomography – based biomarkers

Since its inception (Huang et al., 1991) and introduction into ophthalmology (Fercher et al., 1993), OCT has become the leading diagnostic tool in modern ophthalmology, with the number of applications, indications, and new technologies exponentially rising. Despite the enormous popularity and utility of OCT technology, two fundamental dilemmas have impacted the practical use of OCT significantly: The lack of reliable OCT-based parameters for disease management, and the large amounts of acquired imaging data inaccessible to the physicians' assessment. Both of these critical issues are subject to intensive research and innovation efforts. Currently, a surge of novel evidence suggests a shift of paradigms in the understanding of OCT-based parameters. Specific morphological changes that are relevant for visual function, treatment outcomes, and disease management are increasingly recognized. Moreover, digital technology enabling the comprehensive assessment of "big" OCT data is emerging. The following section reviews OCT-based biomarkers in neovascular AMD and highlights the vital role of OCT in disease management. Fig. 2 illustrates key imaging biomarkers in high-resolution OCT of neovascular AMD.

6.1. Central retinal thickness

The easiest and most obvious way to quantify retinal changes in OCT data is the measurement of retinal thickness (Hee et al., 1995). From the earliest commercial OCT systems onwards, manufacturers have provided integrated automated software algorithms capable of segmenting the internal limiting membrane (ILM) and the retinal pigment epithelium (RPE) or Bruch's membrane as the inner and outer retinal boundaries. Derived retinal thickness measurements at several locations can be represented as appealing thickness maps, with the aim to allow a clinical judgement of disease activity at a single glance. Central retinal thickness in particular, the average thickness in a circular field of 1 mm diameter centred on the fovea, was readily embraced both as a quantitative outcome variable in clinical trials and as a measure to gauge treatment effect, allowing retreatment decisions in clinical practice (Fung et al., 2007; Holz et al., 2011). However, the recent years have increasingly provided evidence that retinal thickness is by no means an ideal method to capture morphological changes in neovascular AMD, not to mention patient management.

First, several technical issues limit the applicability and

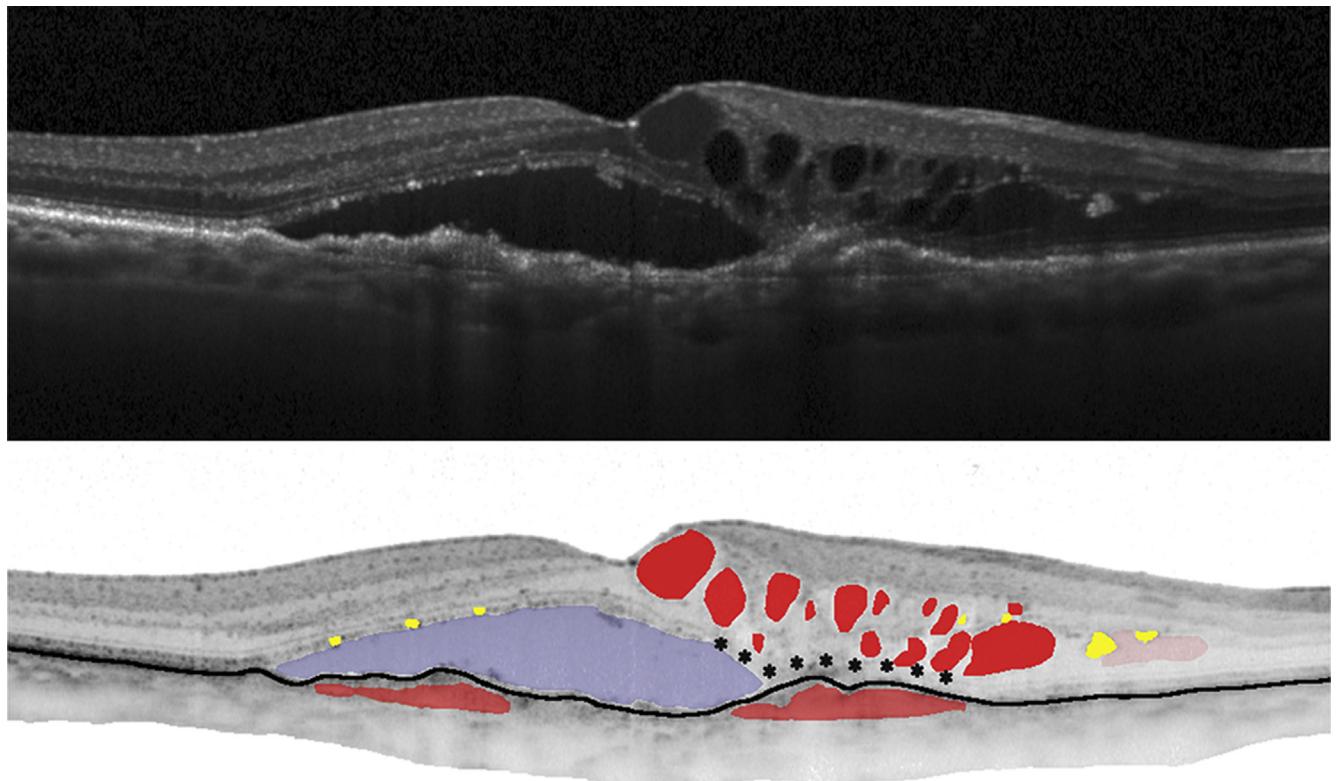


Fig. 2. Typical presentation of neovascular age-related macular degeneration on optical coherence tomography and associated biomarkers. Intraretinal cystoid fluid is highlighted in bright red, subretinal fluid in blue, and pigment-epithelial detachment in dark red. Yellow markings illustrate hyperreflective foci and black asterisks denote alterations in the photoreceptor layers.

reproducibility of retinal thickness measurements. There is a high rate of segmentation errors even in modern OCT devices, which are often clinically relevant, particularly in neovascular AMD (Krebs et al., 2009; Sadda et al., 2006). Second, poor fixation and patient motion may lead to registration errors prohibiting adequate reproducibility over time in longitudinal studies (Ho et al., 2009). Third, comparisons across different OCT devices can be problematic due to the different anatomical structures used for segmentation by the different manufacturers, such as different surfaces of the RPE and Bruch's membrane (Waldstein et al., 2015a). Analysis of OCT data by an independent “reference” algorithm may allow cross-instrument comparisons (Garvin et al., 2008). Investigators have suggested the use of retinal volume instead of retinal thickness, however, as the area of measurement is fixed to the ETDRS-like grid fields, volume measurements are merely a multiplication of average thickness by a (fixed) area, and therefore do not provide additional information.

Clinically, the main drawback of retinal thickness as a measurement variable is that it includes a medley of different retinal compartments and therefore fails to differentiate the subtle changes at the level of the individual pathological components. As shown in Table 1, intraretinal fluid has a negative and subretinal fluid a positive impact on visual outcome, while both components may equally contribute to retinal thickening in the same eye. However, as described in detail in the following sections, changes in the intraretinal compartment for instance may have diametrically different effects on visual function than changes in other retinal regions. These differential effects are lost by averaging over the entire thickness of the retina. Moreover, the relationship between visual acuity and retinal thickness is by no means linear. In contrast, poor visual acuity can be associated with both excessively thick as well as excessively thin retinas (Jaffe et al., 2013).

It is therefore not surprising that retinal thickness offers poor correlations with visual function in neovascular AMD (Keane et al., 2008, 2010; Moutrey et al., 2008; Spaide et al., 2006). While eyes with a thicker retina demonstrate poorer visual acuity at the treatment-naïve stage, this association is generally lost after a few anti-VEGF treatments and is therefore inadequate for follow-up monitoring (Simader et al., 2014). Central retinal thickness has been used successfully for monitoring and retreatment indications in the PRONTO study in a small cohort of patients and as a single component within a long list of other retreatment criteria (Fung et al., 2007; Lalwani et al., 2009), but these findings failed to be replicated on the large scale. The fact that CRT has been the major OCT-based retreatment indicator by protocol for retreatment decisions in flexible regimens in the recent treatment trials supported the incorrect notion that PRN in general fares inferior to a fixed retreatment regimen (Holz et al., 2011).

Clinical implications

Due to poor reproducibility, lack of correlation with relevant functional outcomes, and low sensitivity for subtle changes in the retinal compartments, it is not recommended to base clinical decisions or trial outcomes on retinal thickness measurements.

6.2. Intraretinal cystoid fluid

According to Gass, one of the hallmark events in the pathogenesis of neovascular AMD is the disruption of the external limiting membrane–photoreceptor complex by invasion and proliferation of the CNV lesion, and resultant leakage of fluid into the neurosensory retina (Gass, 1998). On OCT, intraretinal accumulation of fluid appears as diffuse retinal thickening, or more frequently, as hyporeflective cystoid spaces. Such intraretinal cystoid fluid (IRC) is to date the most important predictive factor both

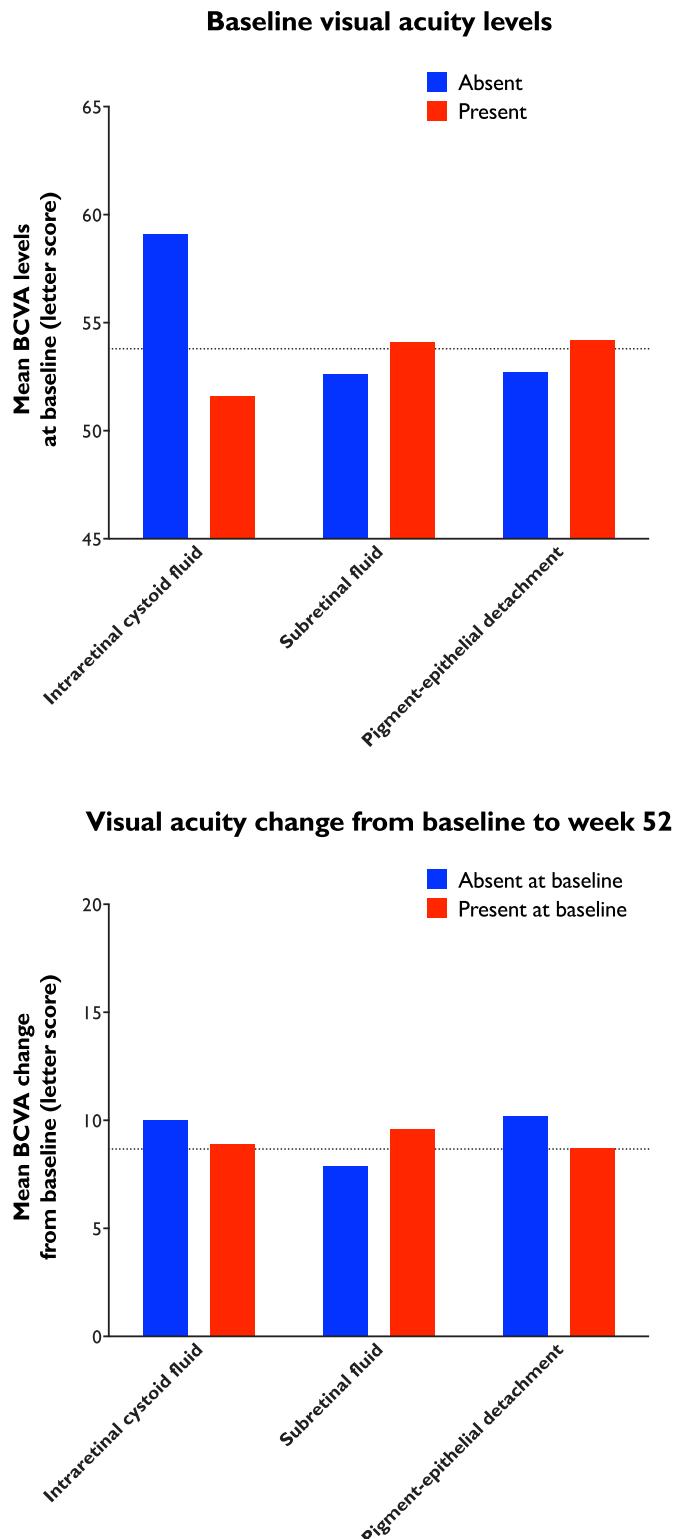


Fig. 3. Impact of retinal morphology on visual function in neovascular age-related macular degeneration. It is important to differentiate between biomarkers for baseline visual acuity (left) and biomarkers for visual acuity change over time (right). Intraretinal cystoid fluid is associated with reduced visual acuity levels at baseline as well as slightly reduced visual acuity gains during therapy. Subretinal fluid in contrast is correlated with increased visual acuity gains. Pigment-epithelial detachment is associated with slightly reduced visual acuity gains over time. The dotted lines indicate the mean visual acuity (gain) for all patients. Graph based on data of over 2400 patients enrolled in the VIEW trials (Waldstein et al., submitted for publication-b).

for baseline VA as well as for visual acuity outcomes in neovascular AMD treatment. Ancillary quantitative studies found that up to 60% of the actual visual acuity in eyes with treatment-naïve neovascular AMD could be explained by cystoid changes in the neurosensory layers (Waldstein et al., submitted for publication-a).

A large number of studies have investigated the role of IRC on visual function and treatment outcomes. Although all studies are retrospective, several are post-hoc analyses of prospectively collected data with assessments performed by certified reading centres, adding strength to these analyses. In the typical treatment-naïve neovascular AMD study population, the rate of IRC prevalence at the initial presentation ranges from 52% to 76% (Jaffe et al., 2013; Simader et al., 2014; Waldstein et al., submitted for publication-b). In terms of the angiographic classification of choroidal neovascularization in AMD, IRC is mostly associated with classic or RAP lesions, or with late-stage occult lesions where the neovascular network has breached its confined sub-RPE space and impairs the support of overlying neurosensory retina. In the combined OCT – angiography classification according to Freund, IRC is a hallmark of Type II and III lesions, as well as of late-stage Type I lesions (Freund et al., 2010; Nagiel et al., 2015). It can therefore be concluded that IRC is both a sign of a more aggressive lesion type as well as a sign of late presentation in chronic occult CNV.

At the treatment-naïve presentation, eyes with IRC show reduced visual acuity by a mean of approximately two lines on ETDRS charts (Jaffe et al., 2013; Ritter et al., 2014; Schmidt-Erfurth et al., 2015; Simader et al., 2014; Waldstein et al., submitted for publication-b). Similarly, patients presenting without cystoid changes show markedly better visual function than an average study population. A reduction in retinal function associated with IRC has also been demonstrated for macular sensitivity using microperimetry (Sulzbacher et al., 2012, 2013). The functional disadvantage of eyes with IRC at baseline persists during therapy. Mean BCVA changes in eyes with IRC are generally somewhat lower than in eyes without IRC, particularly when balanced for baseline visual acuity (Schmidt-Erfurth et al., 2015). Fig. 3 illustrates mean BCVA levels in eyes with or without IRC.

Not all intraretinal fluid on OCT is caused by active CNV-associated exudation, and it is of great importance to differentiate between cystoid fluid caused by exudative CNV ("exudative IRC") and cystoid fluid associated with neurosensory degeneration ("degenerative IRC"). Exudative IRC are relatively large circular or ovoid spaces often associated with pigment epithelial detachments (Type I or III lesions) or neovascular tissue (Type II CNV). They are exquisitely responsive to anti-VEGF treatment. Studies have demonstrated an almost complete reduction of exudative IRC one week after a single anti-VEGF injection (Bolz et al., 2010). Furthermore, a reduction in exudative IRC is directly and strongly associated with visual acuity gains (Waldstein et al., submitted for publication-a), mandating proactive anti-VEGF treatment during the loading phase.

Degenerative IRC (or "cystic degeneration") are typically small, sharply demarcated hyporeflective spaces overlying regions of dysfunctional RPE, which can either manifest as RPE atrophy or scarring (Gianniu et al., 2015; Querques et al., 2011). Degenerative IRC may even occur in non-neovascular AMD without any evidence of leakage (Cohen et al., 2010; Göbel et al., 2014). The current hypothesis for this finding is that once the RPE has lost its photoreceptor-supportive capabilities, progressive degeneration leads to a loss of neurosensory elements and passive accumulation of serous fluid, similar to a sponge. Degenerative IRC are not a sign of active disease and do not respond to anti-VEGF treatment – even most intensive monthly therapy (Gianniu et al., 2015; Schmidt-Erfurth et al., 2015). Continued intravitreal treatment is not warranted solely for degenerative intraretinal fluid. Analysing the

integrity/destruction of the underlying RPE layer on OCT can make a clinical distinction. Adding to the negative role of IRC in general, eyes presenting with degenerative IRC persisting beyond the loading phase have an even further reduced visual prognosis by approximately one ETDRS line (Schmidt-Erfurth et al., 2015).

Almost all studies of IRC in neovascular AMD use a dichotomous classification of IRC presence/absence. Only a few pioneering works have attempted to quantify IRC in OCT, a time-consuming effort that will be aided in the future by computerized quantification methods for IRC (Kashani et al., 2009; Schlegl et al., 2015). Studies quantifying IRC in three-dimensional SD-OCT have concluded that the amount of IRC is linearly correlated with visual function at the treatment-naïve stage (Waldstein et al., submitted for publication-a). In detail, the horizontal extension (i.e. the area) covered by IRC was more relevant to visual function than the volume or vertical extension beyond a 20- μm threshold (Roberts et al., 2014; Waldstein et al., submitted for publication-a). This corroborates pathophysiological hypotheses proposed for eyes with cystoid macular oedema suggesting that cystoid fluid-mediated neurosensory damage may be caused by alterations of bipolar axons (Pelosini et al., 2011). In line with this theory, there is compelling evidence that a proportion of the neurosensory damage caused by intraretinal cystoid fluid is not reversible by treatment (Jaffe et al., 2013). Accordingly, quantitative studies have demonstrated that about 20% of visual acuity outcomes are already determined by irreversible cyst-mediated neurosensory damage at baseline, irrespective of the intensity of anti-VEGF therapy (Waldstein et al., submitted for publication-a). Individualized prognostic planning will therefore likely be based on quantification of retinal morphology in the future.

Clinical implications

The most important clinical message conveyed by the current data on intraretinal cystoid fluid is that patients with neovascular AMD should be diagnosed and treated early. As the majority of eyes present with Type I (sub-pigmentepithelial) lesions, cystoid changes occur after long-standing disease with invasive growth beyond the sub-RPE space. Care should be taken to detect and treat active CNV before the development of intraretinal fluid, as “watchful waiting” may lead to irreversible neurosensory damage. Second, patients presenting with extensive foveal cystoid fluid may be counselled that, though they are likely to experience some gain in visual acuity, even aggressive treatment may not provide similar levels of functional benefit as in the average patient without such morphologic changes. Finally, anti-VEGF treatment may be stopped for cystic degeneration (“degenerative IRC”) overlying RPE atrophy or scarring due to the limited responsiveness of such fluid and an unfavourable overall functional prognosis, saving efforts for patients and budgets.

6.3. Subretinal fluid

Subretinal fluid (SRF) is a particularly intriguing imaging biomarker in the sense that it is the only “pathologic” morphologic parameter consistently associated with positive effects on VA. The evidence that SRF may be associated with better visual function and more benign disease courses has recently been supported by several post-hoc analyses.

In typical phase III trials, 70%–85% of patients present with SRF at the time of enrolment (Jaffe et al., 2013; Simader et al., 2014; Waldstein et al., submitted for publication-b). The finding of subretinal fluid is associated with all lesion types and is typically the first exudative sign in Type I lesions (Freund et al., 2010). Concerning the effect of SRF on visual function, numerous large studies have demonstrated that the presence of subretinal fluid at any time is associated with higher VA levels (Jaffe et al., 2013; Schmidt-

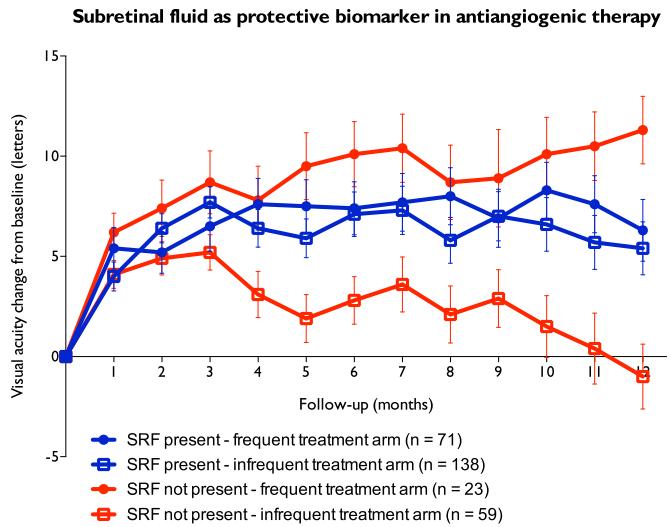


Fig. 4. Role of subretinal fluid as a treatment-modifying imaging biomarker. In patients with subretinal fluid at baseline (blue graphs), antiangiogenic therapy leads to identical visual acuity outcomes, regardless of treatment regimen (monthly versus every 12 weeks dosing). In contrast, patients without subretinal fluid at baseline (red graphs) demonstrate unfavourable outcomes if treatment was not administered on a monthly basis. Figure redrawn from (Waldstein et al., submitted for publication-c), error bars indicate the standard error of the mean.

Erfurth et al., 2015). Moreover, patients with subretinal fluid derive larger visual acuity benefits from antiangiogenic treatment (Schmidt-Erfurth et al., 2015; Dirani et al., 2015a). In addition, eyes with SRF are less likely to develop RPE atrophy even under an intensive monthly anti-VEGF regimen (Sadda et al., 2014; Sato et al., 2015).

As a potential explanation for the positive effects of SRF on visual function and maintenance of a viable RPE as outlined above, we hypothesize that the presence of SRF could be suggestive of a functional, i.e. perfused neovascular net and/or choriocapillary layer in the foveal area providing RPE and photoreceptor survival in contrast to advanced vascular atrophy in the sub-RPE space. In a hypoxic environment such as in AMD, a perfused CNV lesion may be considered a “survival factor” for RPE/photoreceptor viability. The presence of SRF without the simultaneous manifestation of intraretinal fluid may be suggestive of a less aggressive, perhaps even “supportive” stage of CNV rather than advanced, destructive neurosensory ingrowth associated with intraretinal exudation. This is supported by the fact that treatment-refractory SRF was not detrimental to vision outcomes in a recent study (Giannou et al., 2015). On the other hand, complete CNV regression was demonstrated to correlate with RPE/photoreceptor atrophy and vision loss (Channa et al., 2015). Another possible explanation for the positive effects of SRF may be that SRF tends not to be directly co-localized with IRC and PED (data on file). This may indicate that in eyes with subfoveal SRF, the CNV lesion is located extrafoveally, with fewer effects on BCVA. Further studies are required to elucidate the pathophysiologic background behind the positive phenomena associated with SRF. OCT angiography (Section 7.2.2) may aid in providing functional information on CNV perfusion status in this respect. Interestingly, investigators also recently reported a positive effect of SRF on visual outcomes for other disease entities, i.e. diabetic macular oedema and retinal vein occlusions (Liu et al., 2015; Sophie et al., 2015). Fig. 3 illustrates mean BCVA levels and BCVA change in eyes with or without SRF.

Subretinal fluid in neovascular AMD does not only seem to positively influence visual function, but also the need for retreatment. In a post-hoc analysis comparing the outcomes of fixed

frequent versus infrequent anti-VEGF treatments, eyes with SRF had similarly favourable visual acuity outcomes regardless of the treatment regimen. In contrast, eyes without SRF at baseline showed much poorer outcomes if treated infrequently than if treated frequently (Waldstein et al., submitted for publication-c). These findings imply that the absence of SRF may represent a particularly advanced disease subtype in neovascular AMD, or that CNV in eyes with SRF may be less dependent on VEGF, as a less intensive VEGF inhibition may be able to achieve acceptable disease control. Fig. 4 illustrates visual acuity over time in eyes with and without SRF at baseline in frequent versus infrequent anti-VEGF treatment.

Quantitative studies have revealed that the amount of SRF may correlate positively with visual acuity (Waldstein et al., submitted for publication-a). Automated quantification of SRF by computerized segmentation has been proposed recently (Schlegl et al., 2015). Some studies have investigated the optical density of SRF lesions, concluding that an increased reflectivity in SRF is associated with poorer visual function and worse treatment outcomes (Ahlers et al., 2009; Neudorfer et al., 2012). It should however be noted that optical density assessments in OCT are somewhat problematic due to the inadequate capability to normalize the signal passing through different ocular tissues at different locations with various light-tissue interactions. Although SRF usually responds to treatment very rapidly (with maximum reductions reached after three monthly injections (Waldstein et al., submitted for publication-b)), SRF may be refractory to treatment in a subgroup of patients; however, this was found not to be associated with an adverse visual prognosis (Giannou et al., 2015).

Clinical implications

Current data suggest that eyes with SRF at presentation are likely to exhibit a comparably benign disease course, manageable by anti-VEGF injections with extended intervals up to every 12 weeks. As such, eyes with SRF may be the ideal candidates for treat-and-extend regimens. However, prospective studies should be conducted to validate these results for treatment recommendations based on top-level evidence.

6.4. Alterations of outer retinal layers

Neovascular invasion and fluid exudation can cause extensive damage at the level of the photoreceptor layers, leading to profound functional losses. OCT can detect such changes as signal alterations in the hyperreflective bands of the outer retina. Controversy surrounds the nomenclature of the hyperreflective bands and their correlation with anatomical structure (Spaide and Curcio, 2011). In this article, the first hyperreflective band is referred to as "external limiting membrane", and the third band is referred to as "ellipsoid zone" of the photoreceptor inner segments according to the international nomenclature for OCT panel recommendations (Staurenghi et al., 2014).

Several studies report a significant association between the condition of the external limiting membrane and ellipsoid zone on OCT with visual function in neovascular AMD (Keane et al., 2012). However, the major limitation of the outer retinal bands as imaging biomarkers in neovascular AMD is the challenge in reliably quantifying the often subtle contours. Thus, published studies generally suffer from small sample sizes and qualitative assessments in single OCT slices, further reducing reproducibility.

Despite the poor reproducibility and limitations in current assessment strategies, the magnitude of effect of photoreceptor alterations on visual function seems substantial. A study in 40 treatment-naïve eyes with neovascular AMD detected a significant correlation between the extent of external limiting membrane disruption and VA with $R^2 = 0.5$ and a large difference of 40 letters

VA score between patients with intact external limiting membrane and patients with poor external limiting membrane status (Akagi-Kurashige et al., 2012; Shin et al., 2011). Similar findings were reported for the ellipsoid zone in eyes after PDT treatment (Hayashi et al., 2009; Oishi et al., 2010), for retinal sensitivity (Roberts et al., 2014; Sulzbacher et al., 2012), and in quantitative studies (Ristau et al., 2014). However, unlike other factors such as IRC and SRF, the outer retinal status at baseline was not found to be predictive of the change in visual acuity during therapy (Kim et al., 2012; Mathew et al., 2013). Antiangiogenic therapy can result in restoration of the photoreceptor signal, with associated improvement in visual function (Kim et al., 2012; Oishi et al., 2013; Sulzbacher et al., 2013).

Clinical implications

Current evidence suggests that the presentation of the outer retinal bands on OCT appears to be a useful biomarker for visual function at the treatment-naïve stage. However, its power to predict visual acuity change over time during therapy appears not to surpass the predictive value of baseline VA alone, and therefore other biomarkers such as IRC and SRF may be more relevant in individualizing treatment approaches. Efforts to automatically quantify photoreceptor changes in OCT may improve the reproducibility of photoreceptor assessments in the future (Chen et al., 2012; Zhang et al., 2014).

6.5. Hyperreflective foci

A typical OCT sign in neovascular AMD is the appearance of small, hyperreflective dots ("hyperreflective foci") in the neurosensory retina, particularly adjacent to fluid lesions (Keane et al., 2012). There is controversy regarding the pathomorphologic origin and role of these foci. Proposed anatomical correlates include migrating RPE cells or pigment-laden macrophages (Ahlers et al., 2010), microexudates of lipid or fibrin (Bolz et al., 2009), or activated microglia (Coscas et al., 2013). In early AMD, hyperreflective foci are a risk factor for progression to advanced disease and co-localize to pigmentary abnormalities, which suggests that an RPE-related mechanism such as RPE migration may at least in part be involved in the pathogenesis of these findings (Christenbury et al., 2013; Folgar et al., 2012). Dissociation of RPE cells from their original epithelial monolayer as sloughing, sledging, and migration has been shown to be associated with disease progression in AMD (Curcio et al., 1998). In early AMD, RPE dislocation is associated with a conversion towards advanced, atrophic or neovascular, stages of AMD (Christenbury et al., 2013). Hyperreflective foci may be an early sign of Type III (RAP) neovascularization (Nagel et al., 2015). In chronic neovascular AMD cases, hyperreflective foci may be co-localized with extensive accumulations of fluid and hard exudates, a phenomenon that has been termed the "pearl necklace" sign (Gelman et al., 2014).

Studies have reported that hyperreflective foci were associated with poorer VA outcomes in the treatment of neovascular AMD (Akagi-Kurashige et al., 2012). Their resolution was prognostic of visual acuity gain in another prospective study, probably representing resolution of lipid exudation with inactivation of the CNV lesion (Coscas et al., 2013).

Clinical implications

The limited available data suggest a potential role of hyperreflective foci as a biomarker for lesion activity and stage. Further quantitative studies are needed to corroborate this finding.

6.6. Outer retinal tubulation

Outer retinal tubulation on optical coherence tomography represents a hyporeflective, branching tubular structure surrounded

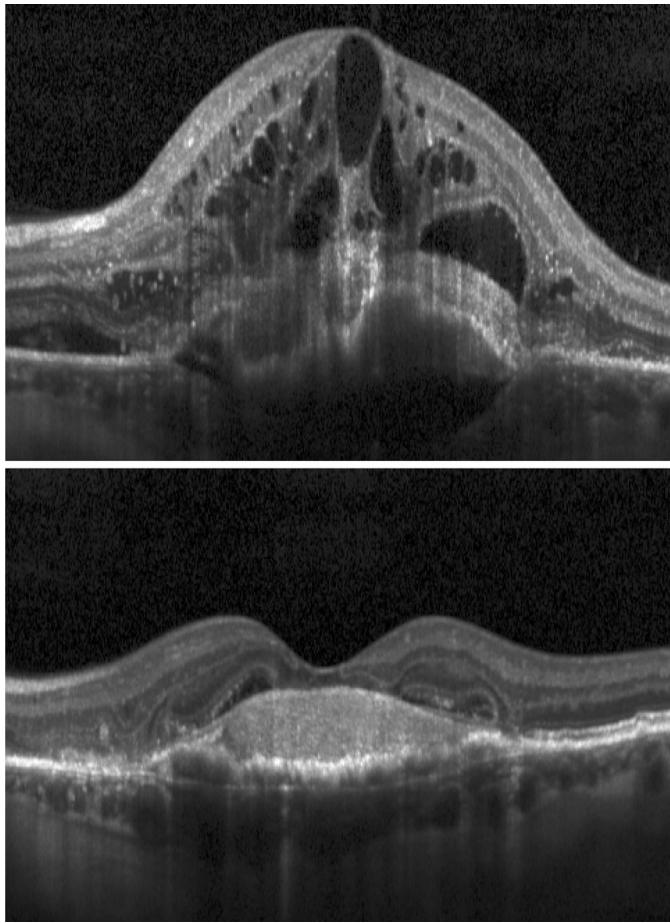


Fig. 5. Outer retinal tubulation and subretinal scarring as biomarkers for severely destructive neovascular disease. **Top:** Baseline presentation of a patient with neovascular age-related macular degeneration. Extensive intraretinal cystoid fluid can be seen overlying ill-defined subretinal hyperreflective material in conjunction with a fibrovascular pigment-epithelial detachment. Contractile elements in the fibrovascular membrane have caused outpouching of Bruch's membrane, termed a prechoroidal cleft. The half-moon shaped fluid pocket on the right represents incipient outer retinal tubulation. Loss of photoreceptor layer signal is widespread throughout the scan. Based on the present imaging biomarkers, prognosis towards visual function is very poor in this condition. **Bottom:** Presentation following long-term vascular endothelial growth factor inhibition. The subretinal hyperreflective material and associated pigment-epithelial detachment have condensed into a spindle-shaped, dense, organized fibrous scar. Outer retinal tubulation can be seen overlying the scar tissue. Despite the lack of other neurosensory pathology, photoreceptor layer loss is widespread and similar in extent to the baseline presentation.

by a hyperreflective ring, located in the outer nuclear layer of the retina and often overlying fibrous scarring (Zweifel et al., 2009). Outer retinal tubulation may be misdiagnosed as intraretinal or subretinal fluid, which lacks the hyperreflective border. It is believed that outer retinal tubulation is a specific pattern of photoreceptor rearrangement in response to injury (Zweifel et al., 2009). Histologically, the hyperreflective border of outer retinal tubulation is composed of external limiting membrane and photoreceptor inner segment mitochondria (Litts et al., 2015a; Schaal et al., 2015). The lumen of outer retinal tubulation can contain photoreceptor outer segments and fluid (Litts et al., 2015a; Schaal et al., 2015). Curcio and associates identified cone residuals in outer retinal tubulation consistent with advanced damage to the foveal retina (Litts et al., 2015b). While the prevalence of outer retinal tubulation is reported to be low in early neovascular AMD (Dirani et al., 2015b), outer retinal tubulation frequently develops over time during antiangiogenic therapy and represents a chronic

and irreversible destruction. The low prevalence of outer retinal tubulation in treatment-naïve CNV may in part be caused by the challenging differential diagnosis with subretinal fluid (Fig. 5). Studies have reported a prevalence of 17% at one year (Dirani et al., 2015b; Lee et al., 2014) and of over 40% at 4 years (Dirani et al., 2015b). Other reports show that outer retinal tubulation is associated with classic-type CNV lesions on fluorescein angiography (Faria-Correia et al., 2013).

As an imaging biomarker, outer retinal tubulation is associated with poorer functional outcomes. Although outer retinal tubulation is not a frequent feature in treatment-naïve eyes, patients with outer retinal tubulation after one year showed a two-line poorer baseline VA score (Faria-Correia et al., 2013; Lee et al., 2014). In terms of visual acuity change during therapy, eyes with outer retinal tubulation showed slightly lower VA gains at one year compared to eyes without outer retinal tubulation (Dirani et al., 2015b; Lee et al., 2014). However, during longer-term follow-up, eyes with outer retinal tubulation demonstrated progressively inferior outcomes (Dirani et al., 2015b). Fig. 5 illustrates outer retinal tubulation development over time in a patient with neovascular AMD.

Clinical implications

Outer retinal tubulation emerged as a biomarker for photoreceptor degeneration in association with reduced visual prognosis. However, further research is needed to define the relevance of this relatively new biomarker in the treatment of neovascular AMD.

6.7. Subretinal hyperreflective material and fibrous scarring

Particularly in Type II (classic) CNV, new vessels from the choroidal neovascular complex typically proliferate directly in the subretinal space after initially penetrating Bruch's membrane (Grossniklaus and Green, 2004). In such cases, the neovascular membrane can be visualized as a poorly defined, medium- to hyperreflective mass between the neurosensory layers and the RPE, termed "subretinal hyperreflective material" (Keane et al., 2012). As the CNV lesion becomes less active during antiangiogenic therapy, the vascular component of the membrane typically regresses or condenses, while the fibrous component remains or often increases, resulting in the formation of a hyperreflective, well demarcated scar (Keane et al., 2012). Several additional lesion components may show a similar appearance to subretinal hyperreflective material in OCT and are usually associated with an active CNV lesion, including subretinal haemorrhage and lipid or fluid exudation (Shah et al., 2014). Subretinal hyperreflective material is reported to be extremely frequent in Type II and III CNV lesions, and much less common in Type I (occult) lesions (Liakopoulos et al., 2008). In CATT, 77% of eyes showed subretinal hyperreflective material at the time of enrolment, with a decrease to 54% after two years of treatment (Willoughby et al., 2015). Multimodal imaging studies demonstrated that subretinal hyperreflective material might be associated with leakage activity or rather progressive staining on fluorescein angiograms, particularly in the case of poorly defined borders and low reflectivity levels (Giani et al., 2011a, 2011b).

In terms of visual function, investigators reported an association between an increased thickness of subretinal hyperreflective material and reduced visual acuity levels (Jaffe et al., 2013; Ristau et al., 2014). Quantitative studies showed a 14 letters difference in BCVA between eyes without subretinal hyperreflective material, and eyes with the highest extent of subretinal hyperreflective material ($>1000 \mu\text{m}$ in diameter, involving the foveal centre) (Willoughby et al., 2015). Moreover, contrast sensitivity may be reduced in the presence of subretinal hyperreflective material (Keane et al., 2010). In a more general definition of functional outcomes, another study

identified subretinal hyperreflective material as a predictive factor for non-responders (Byun et al., 2010). Furthermore, subretinal hyperreflective material at baseline was associated with scar development and sustained loss of visual acuity in CATT (Daniel et al., 2014; Ying et al., 2014).

The development of a fibrotic and/or atrophic scar (secondary to or consistent with subretinal hyperreflective material) typically leads to substantial visual acuity loss. The reported magnitude of effect of scar development on VA outcomes was approximately 10 ETDRS letters in a large-scale analysis (Bloch et al., 2013b). In extrafoveal scars, the distance between the scar edge and the foveal centre was predictive of visual acuity (El-Emam et al., 2013). Fig. 5 demonstrates the development of subretinal hyperreflective material into fibrous scarring over time.

Clinical implications

The presence of subretinal hyperreflective material and subsequent development of fibrous scarring is a major risk factor associated with sustained VA loss in the treatment of neovascular AMD. New pharmacologic agents directed against scar development may provide additional benefit in the therapy of neovascular AMD (Tolentino et al., 2015).

6.8. Pigment epithelial detachment

A veritable paradigm change has recently established pigment-epithelial detachment (PED) as a critical biomarker in the management of neovascular AMD. Traditionally, clinicians have not focused on PED and associated sub-pigmentepithelial fluid in the decision algorithms for treatment indications, and none of the large-scale prospective treatment trials have included PED into their retreatment criteria as per protocol. However, recent studies revealed that PED-associated neovascular reactivations leading to exudative recurrences are a major culprit for long-term vision loss in individualized anti-VEGF therapy. Therefore, it is recognized today that PED, which harbours the primary neovascular lesion, is an extremely relevant disease component for patient management.

PED was present in 54%–80% of patients at the time of enrolment in CATT, EXCITE, and VIEW (Jaffe et al., 2013; Simader et al., 2014; Waldstein et al., submitted for publication-b), depending on reading-centre specific OCT-based diagnostic criteria. These numbers include all morphologic subtypes of PED, such as serous PED (filled with optically empty-appearing fluid), fibrovascular PED (filled with heterogeneously hyperreflective material) and mixed-type PED. In Type I or occult CNV, PED represents the primary disease component, with secondary accumulation of SRF and IRC only in late disease stages (Freund et al., 2010). In fact, in these

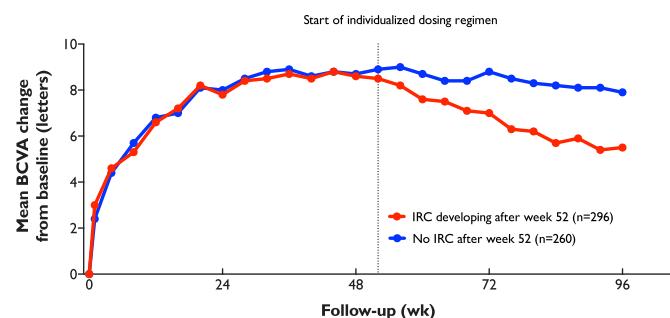


Fig. 6. Pigment-epithelial detachment as risk factor for vision loss during individualized dosing. In the VIEW studies, patients received continuous anti-VEGF therapy during the first 48 weeks. At 52 weeks, a discontinuous, “as-needed” dosing regimen was introduced. Only in a precisely defined patient population, i.e. eyes with pigment-epithelial detachments developing secondary intraretinal cystoid fluid (IRC, red graph), the reactive dosing regimen led to pronounced vision loss.

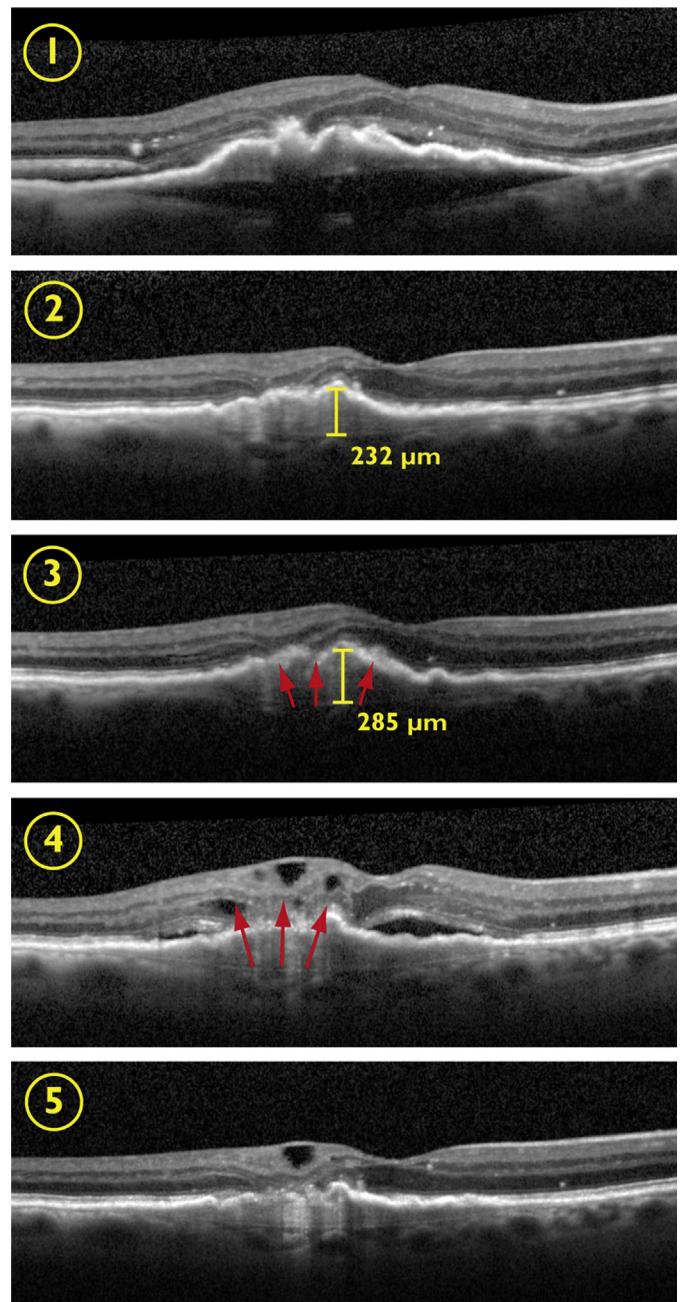


Fig. 7. Exemplary disease course illustrating the pathogenetic concept of pigment-epithelial detachment and secondary cyst development as a risk factor for vision loss during a PRN regimen. 1) Baseline presentation of a patient with Type I choroidal neovascularization. The neovascular membrane is visible as hyperreflective tissue adherent to the inner leaflet of the retinal pigment epithelium. 2) A course of intensive intravitreal therapy achieves a dry retina. However, an elevation of the retinal pigment epithelium corresponding to the underlying fibrovascular tissue remains. As the anatomical situation is satisfactory, therapy may be stopped and monitoring of the patient continues. 3) At a subsequent visit, growth of the pigment-epithelial detachment is documented. This is equivalent to an early, “silent” recurrence of choroidal neovascularization. As the patient is not symptomatic, most protocols would not indicate retreatment at this stage. 4) One month later, overt recurrence with intraretinal and subretinal fluid has developed. Intraretinal cystoid fluid causes neurosensory disruption and vision loss. 5) Despite repeated antiangiogenic treatment, the functional deficit incurred by the fluid recurrence may not be completely restored. In this patient, cystoid degeneration developed overlying an area of pigment epithelial atrophy, as visible by the signal transmission enhancement.

lesions the CNV membrane undermines the RPE and adheres to the inferior surface of the elevated RPE monolayer (Rahimy et al., 2014). PED is also a defining feature in Type III CNV lesions (Nagiel et al., 2015).

A course of three monthly anti-VEGF injections generally reduces the rate of PED by about 25%, in contrast to a 70–80% resolution of sub- and intraretinal fluid (Waldstein et al., submitted for publication-b). By PED subtype, purely serous PED typically disappears completely and rapidly (Dirani et al., 2015a; Nagiel et al., 2015). The exceedingly more frequent fibrovascular-type PED often collapses, but a chronic RPE-elevation caused by underlying fibrovascular membranes persists. This is confirmed by the fact that an irregular RPE surface is often detected following resolution of the sub-RPE fluid components. The fibrovascular tissue confined under the RPE leaflet may be configured in a layer-like, organized fashion and may, upon shrinkage of contractile elements in the fibrovascular membrane, be associated with a pre-choroidal cleft (Rahimy et al., 2014).

Concerning the impact on vision, PED *per se* seem to cause only minor changes in visual function (mainly metamorphopsia), which is probably the main reason why this disease component has often been neglected previously. While the neovascular disease remains confined to the sub-RPE space, viable photoreceptors and neurosensory retina initially enable unaltered visual performance. In the typical neovascular AMD study population, eyes with PED at the treatment-naïve stage on average even demonstrated slightly better visual acuity than eyes without PED (Jaffe et al., 2013; Waldstein et al., submitted for publication-b). On the other hand, the presence of PED was associated with slightly reduced visual acuity gains over time (Schmidt-Erfurth et al., 2015), leading to identical VA outcomes at 52 weeks of treatment, regardless of PED presence. Fig. 3 illustrates mean BCVA levels in eyes with or without PED.

The clinically important role of PED is unveiled only when a flexible PRN regimen adds physician-determined retreatment indications and discontinuous retreatment intervals. While on average all patients lost vision over time in most PRN-based treatment trials (Busbee et al., 2013; Holz et al., 2011; Martin et al., 2011; Schmidt-Erfurth et al., 2014b), a recent post-hoc analysis demonstrated that the only morphologic subgroup experiencing visual acuity loss in PRN treatment constituted eyes with primary PED at baseline and secondary IRC developing during PRN therapy (Fig. 6, (Schmidt-Erfurth et al., 2015)). As PED was traditionally not considered as a retreatment indication in most PRN protocols, progressive decompensation of untreated PED lesions with neovascular growth and secondary development of functionally degrading intraretinal fluid seems to be the key driver of long-term vision loss in this patient population (de Amorim Garcia Filho et al., 2013; Penha et al., 2013; Schmidt-Erfurth et al., 2015). The sequence of events may follow a typical pattern of delayed retreatment of sub-pigmentepithelial CNV recurrence: After an intensive course of anti-VEGF injections, patients present with a rather flat, homogeneously hyperreflective RPE elevation with a completely dry overlying neurosensory retina. Encouraged by the appealing anatomic result, treatment is paused and patients are followed by OCT-based monitoring. Consecutively, the sub-pigmentepithelial CNV reactivates and first causes slow growth of the PED lesion harbouring the underlying neovascular net. OCT angiography may reveal persistent CNV components within PED-like RPE lesions and allow to identify the risk for neovascular recurrence before intraretinal leakage may occur. The role of PED in disease progression highlights the established experience that VEGF inhibition alone is unable to eliminate the CNV component on the long-term, but is rather limited to anti-leakage effects. As this may not be recognized clinically as a retreatment indication, such

patients may be deferred to monitoring only. The consequences of delayed treatment are CNV reactivation, allowing further neovascular growth, and intraretinal cystoid fluid accumulation causing progressive neurosensory damage and vision loss (Gerdin et al., 2011). Although patients are treated as soon as intraretinal fluid is detected, some functional loss remains permanent and culminates in a steady visual decline. Fig. 7 illustrates the pathophysiological concept of progressive VA decline in patients with PED caused by recurrent intraretinal cystoid fluid.

Larger PEDs are an important risk factor for the development of RPE tears, a severe complication in neovascular AMD with often poor functional outcomes (Sarraf et al., 2014). Sarraf and co-workers have identified several specific PED characteristics conveying a higher risk for RPE tears, including a PED height of >600 µm, a PED diameter >5 mm, and the presence of a hyperfluorescent “ring” around the border of the PED in fluorescein angiography analysis (Chiang et al., 2008; Sarraf et al., 2013). They hypothesized that RPE tears may develop by contraction of Type I neovascular membranes at the inner leaflet of the PED (Nagiel et al., 2013). There appears to be a clear causative association between RPE tears and anti-VEGF therapy, with such tears typically occurring within the first three antiangiogenic treatments (Chang and Sarraf, 2007; Sarraf et al., 2014). Regular monitoring and adequate anti-VEGF therapy of continued CNV activity is reported to significantly improve long-term functional outcomes in eyes with RPE tears (Sarraf et al., 2014).

Clinical implications

Based on recent evidence, PED should be included into the retreatment recommendations of flexible antiangiogenic regimens since PED likely harbours persistent neovascular proliferation. During follow-up, PEDs should be carefully monitored by SD-OCT, including quantitative measures (Penha et al., 2012), and any growth in size immediately treated in order to prevent long-term vision loss in flexible treatment strategies. Patients with large PED at presentation (height > 600 µm, diameter > 5 mm) should be counselled about the risk of RPE tear development during the initial anti-VEGF injection series.

6.9. Retinal pigment-epithelial atrophy

Despite the success of antiangiogenic therapy to restore vision and prevent damage associated with CNV, the pathophysiological disease process of non-neovascular AMD inexorably progresses over time, leading to the development of pigment epithelial atrophy also in eyes with neovascular AMD (Kumar et al., 2013). Naturally, the development of confluent areas of RPE cell loss leads to severe visual decline if these areas are located near the foveal centre (Kumar et al., 2013). Similarly, pre-existing geographic atrophy in eyes with CNV is a major factor associated with poor functional outcomes during therapy (Ying et al., 2013).

The main scientific question remaining is whether the development of RPE atrophy may in any form be related or promoted by antiangiogenic therapy itself. The lack of an appropriate, but ethically impossible comparison group of untreated CNV eyes inherently limits studies investigating this issue. Unfortunately, data on the natural history of the progression of RPE atrophy in untreated neovascular AMD are also lacking.

Atrophy of the RPE can be readily assessed by high-resolution OCT as it causes an enhancement of the OCT signal in regions directly below the atrophic area (Keane et al., 2012). The assessments obtained by OCT are directly comparable to conventional autofluorescence measurements (Sayegh et al., 2011), with the added advantages of OCT such as depth resolution and improved diagnostic evaluation of foveal sparing (Forte et al., 2013). The new technology of polarization-sensitive OCT provides intrinsic tissue-

specific contrast for depolarizing melanine-containing vesicles within RPE cells and may be used for precise visualization and measurement of RPE cell loss in neovascular AMD (Ahlers et al., 2010; Pircher et al., 2011; Schutze et al., 2015).

Current evidence suggests that anti-VEGF therapy may lead to a regression of neovascular membranes in some eyes, which is often followed by RPE loss and neurosensory atrophy with or without the development of an atrophic fibrous scar (Channa et al., 2015). The development of RPE atrophy seems to most commonly occur in Type II and III CNV lesions (Grunwald et al., 2014a; Xu et al., 2015a). Studies using advanced polarization-sensitive OCT capable of visualizing viable RPE have demonstrated a loss of RPE cells over time during anti-VEGF treatment, in addition to RPE migration and proliferation, which may be a sign of a certain plasticity of the RPE in neovascular AMD (Schutze et al., 2015). Several studies identified an association between the number of antiangiogenic treatments over time and the growth rate of RPE atrophy (Grunwald et al., 2014a, 2014b; Young et al., 2014). In CATT, the development of geographic atrophy was one of the major causes for sustained visual acuity loss (Ying et al., 2014).

Clinical implications

Progressive RPE atrophy has been identified as a major challenge alongside CNV lesion activity in the management of neovascular AMD. Further studies are needed to define the influence of antiangiogenic substances on RPE cell loss. However, the number of anti-VEGF interventions should be limited to the minimum required to control the disease, while the relationship between VEGF inhibition and RPE atrophy is unclear.

6.10. Choroidal thickness

The advent of specific OCT scanning protocols ("enhanced depth imaging" mode) and the availability of long wavelength (e.g. 1050 nm) OCT have enabled imaging of the choroid and adjacent deep ocular structures with clinical OCT in recent years (Mrejen and Spaide, 2013). When considering choroidal parameters as biomarkers, one must be aware of the extremely high variability of this anatomical structure, which is impacted by age, axial length of the globe, and several environmental factors (Hirata et al., 2011; Ouyang et al., 2011; Wei et al., 2013). Moreover, measurement variability can be substantial (Branchini et al., 2012).

In general, choroidal thickness progressively decreases with age (Wei et al., 2013). Studies have reported that choroidal thickness in neovascular AMD eyes was generally within the normal range, after adjusting for the typical confounding factors (Yiu et al., 2015). Other studies have identified thinner choroids in patients with early AMD (Esmaelpour et al., 2014). Whether choroidal thickness is influenced by anti-VEGF treatment remains controversial. While some studies have demonstrated significant choroidal thinning after a course of VEGF inhibition (Koizumi et al., 2011; Yamazaki et al., 2012), this finding could not be replicated in other reports (Ellabban et al., 2012; McDonnell et al., 2014). One recent study identified choroidal thinning at baseline as a negative prognostic factor for visual acuity gains in the treatment of neovascular AMD, however the analysis did not control for patient age as a confounding factor, and the sample size was limited (Shin et al., 2015).

Clinical implications

The emergence of specific imaging technology to visualize deeper structures has given rise to a large number of studies evaluating the choroid, also in neovascular AMD. However, the available evidence is controversial, which may also be caused by the problematic reproducibility associated with choroidal measurements. Furthermore, better-standardized studies will be required to ultimately define the role of choroidal assessments in neovascular AMD treatment.

6.11. Condition of the vitreomacular interface

For a long time, little consideration has been paid to the ocular compartment located anteriorly to the macular retina and into which the anti-VEGF agent is actually delivered – the vitreous body. Recent evidence demonstrates however, that the condition of the vitreous and the status of the vitreomacular interface are relevant players in the progression of neovascular disease, as well as in the efficacy and durability of action of anti-VEGF treatments.

In the typical neovascular AMD age group, liquefaction of the vitreous core and separation of the vitreous cortex from the retina have already occurred in most patients, leading to the clinical picture of a complete posterior vitreous detachment (Sebag, 2004). A minority of patients present with vitreomacular adhesions or attachment of the vitreous at the optic nerve head with complete vitreomacular separation (Sebag, 2004). Although traditionally in the domain of ocular ultrasonography, the different stages of posterior vitreous detachment can readily be diagnosed using state-of-the-art OCT, preferably using wide scanning angles (also covering the optic disc) and raster patterns (Itakura and Kishi, 2013; Krebs et al., 2011; Mirza et al., 2007). Swept-source OCT offers additional visualization advantages (Spaide, 2014).

Studies report that the rate of posterior vitreous detachment in eyes with neovascular AMD ranges from 60% to 74% (Lee and Koh, 2011; Mayr-Sponer et al., 2013; Waldstein et al., 2014). Vitreomacular adhesion has been reported to be more frequent in eyes with neovascular AMD than in eyes with non-neovascular AMD (Krebs et al., 2007; Lee et al., 2009), however overall incidences seem rather consistent with natural history studies in healthy eyes (Itakura and Kishi, 2013). Prospective studies did not find evidence for a higher risk of CNV development in eyes with vitreomacular adhesion (Waldstein et al., 2012). Manipulation of the vitreous by repeated intravitreal injections is capable of introducing a complete posterior vitreous detachment in eyes with vitreomacular adhesion (Geck et al., 2013; Mayr-Sponer et al., 2013).

Concerning treatment-naïve visual acuity levels, studies report no influence by the vitreomacular interface status (Lee and Koh, 2011; Mayr-Sponer et al., 2013), as long as there are no tractional components to a vitreomacular adhesion (Schulze et al., 2008). Vitreomacular traction should be diagnosed only if the retinal surface is distorted at the insertion site of the vitreous membranes (Duker et al., 2013).

Most importantly, the status of the vitreous has been reported to strongly affect treatment outcomes of anti-VEGF therapy (Lee and Koh, 2011; Mayr-Sponer et al., 2013; Waldstein et al., 2014). Although the data in the literature are somewhat controversial, there is robust evidence that the presence of a posterior vitreous detachment is associated with rather benign disease courses even if treatment intervals are extended up to every 12 weeks dosing (Mayr-Sponer et al., 2013). This is similar to the effect of subretinal fluid, and indeed there may even be some synergy between the two components (Waldstein et al., submitted for publication-c). Patients with both posterior vitreous detachment and SRF at baseline demonstrated very stable visual acuity benefits even with infrequent treatment in a recent post-hoc analysis (Waldstein et al., submitted for publication-c). Eyes without vitreomacular adhesion demonstrated less need for retreatment in a PRN protocol in CATT (Cuilla et al., 2015).

On the other hand, the functional outcomes in eyes with vitreomacular adhesion have been shown to be dependent on the employed treatment regimen (Mayr-Sponer et al., 2013; Waldstein et al., 2014). Excellent visual acuity results have been achieved in eyes with vitreomacular adhesion using a strict monthly dosing protocol or even added verteporfin photodynamic therapy (Mayr-Sponer et al., 2013; Waldstein et al., 2014). Less frequent

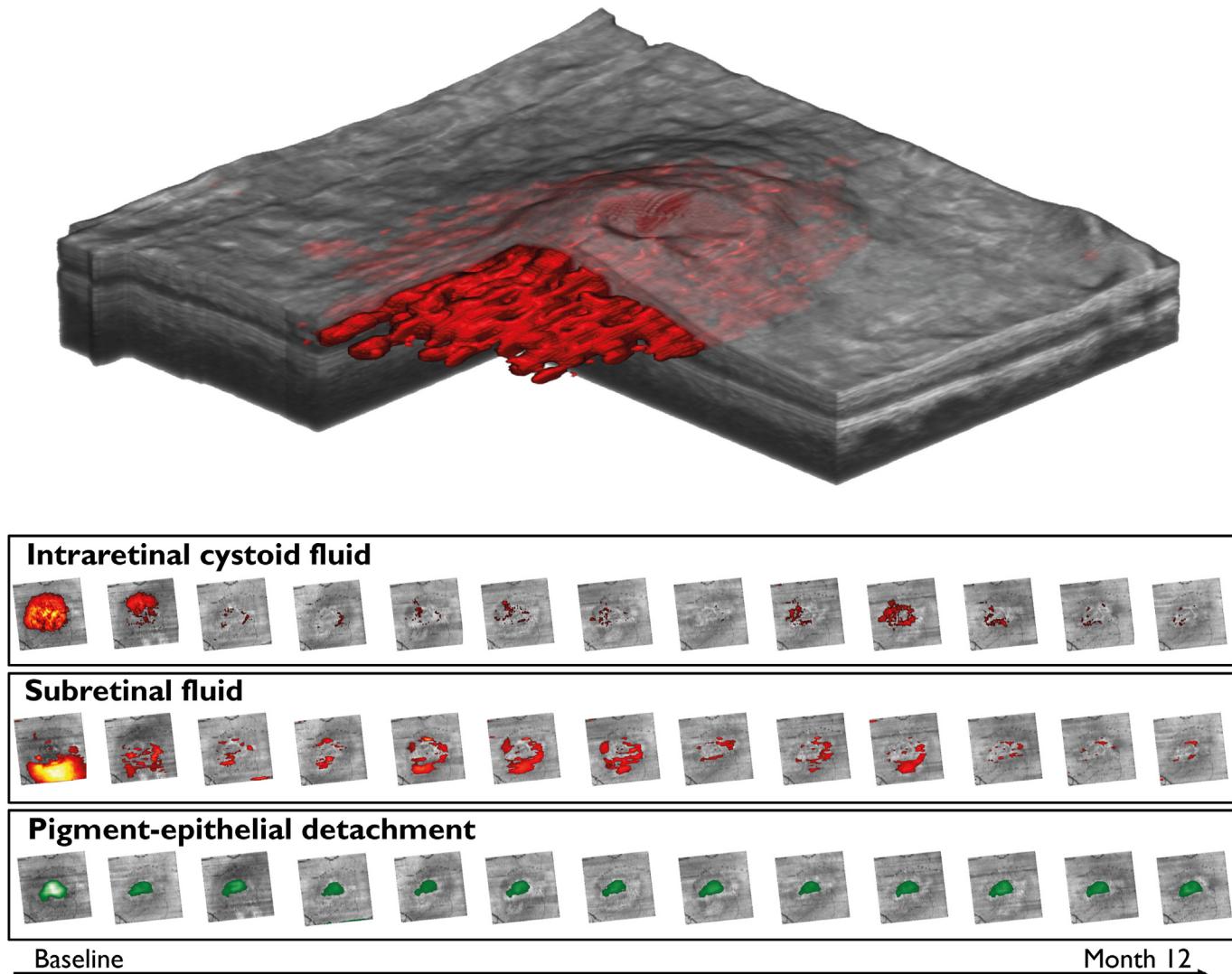


Fig. 8. Computational analysis of OCT biomarkers in neovascular AMD. **Top:** Automated segmentation of SD-OCT volume scans enables a precise quantification of the disease-associated exudative changes. In this example, shown as a 3D rendering, intraretinal cystoid fluid (red) was automatically delineated using a method based on convolutional neural networks (Schlegl et al., 2015). **Bottom:** Accurate segmentation and registration methods allow the assessment of disease courses over time. The amount and distribution of exudative fluid in the individual pathomorphologic compartments of the retina can be visualized in en-face fluid maps. This example demonstrates the typical response- and recurrence patterns of fluid in a patient receiving anti-VEGF therapy. Advanced machine-learning algorithms also enable the prediction of future therapeutic responses based on baseline disease characteristics (Vogl et al., 2015). Figure reprinted from Roberts et al., 2015 (Expert Review of Ophthalmology, Informa Healthcare, in press).

treatment regimens have resulted in unfavourable outcomes in these eyes (Mayr-Sponer et al., 2013).

There are few hypotheses on why the condition of the vitreous shows such a relevant role in anti-VEGF therapy. Some authors proposed potential pharmacokinetic interactions between the vitreous and the anti-VEGF substance, including altered drug diffusion into the retina (Goldenberg et al., 2008; Mayr-Sponer et al., 2013). Moreover, a greatly increased drug clearance has been demonstrated for vitrectomized eyes (Ahn et al., 2014; Christoforidis et al., 2013). Most interestingly, reduced cytokine levels, including lower levels of VEGF, have been reported in eyes with posterior vitreous detachment (Takahashi et al., 2015). Mechanical forces leading to poorer responses in eyes with vitreomacular adhesion seem less likely since these eyes allow optimal visual benefits if treated aggressively (Lee and Koh, 2011). Further experimental studies are required to shed light onto this important topic.

Clinical implications

Based on the current retrospective data showing benign disease courses in patients with complete posterior vitreous detachment,

such patients may be recommended a treat and extend regimen, particularly if SRF is also present at baseline. On the other hand, patients without a complete posterior vitreous detachment should be treated intensively and aggressively to avoid possible functional losses with infrequent therapy. Prospective studies should follow to allow recommendations based on higher levels of evidence.

7. Conclusion and future directions

The advent of high-resolution, three-dimensional OCT has pushed the door wide open for a bright future of biomarkers in clinical ophthalmology, and in particular in the management of neovascular AMD. In addition to clinical factors such as age, visual acuity, and genetic background, a wealth of imaging-derived, quantifiable biomarkers with substantial relevance for visual function and treatment outcomes has been identified as described in this article. A combination of the foremost relevant biomarkers including intraretinal cystoid fluid, subretinal fluid, pigment-epithelial detachment, and vitreomacular interface configuration

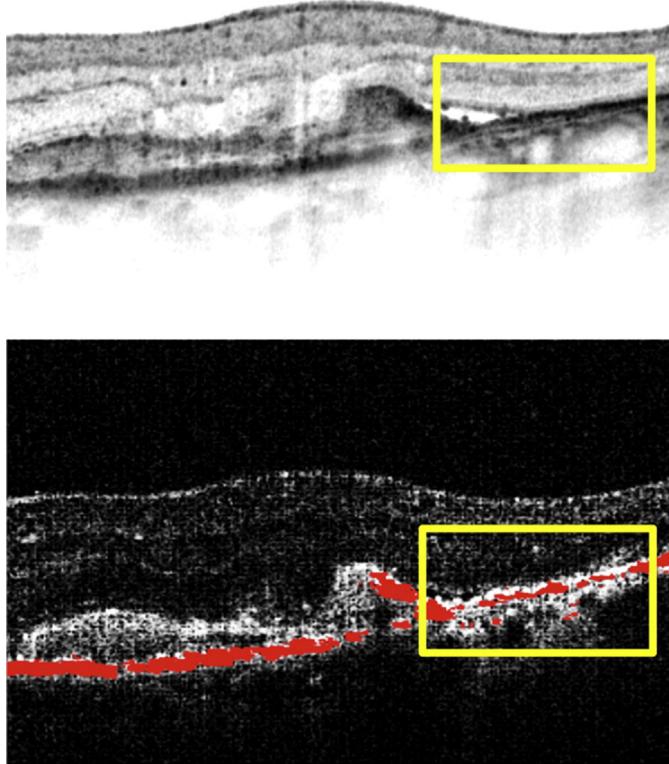


Fig. 9. Polarization-sensitive OCT to image retinal pigment epithelial integrity. The diagnosis of subtle RPE cell loss is challenging in conventional intensity-based OCT (Top). Within the region of interest (yellow box), the RPE layer appears regular, although subtle transmission defects are present. In contrast, the intrinsic depolarization information provided by PS-OCT (red overlay) identifies severe RPE-irregularity (Bottom). Figure reprinted from Schütze et al. (2015).

may be able to efficiently personalize prognosis and disease management in the near future.

7.1. Computational analysis of ophthalmic imaging data

The remaining fundamental problem of modern OCT technology

is that it captures such vast amounts of data, that they cannot be meaningfully evaluated in a clinical setting. A promising new horizon in this dilemma is the introduction of computational methods for OCT analysis (Fig. 8), which are the only way to fully exploit the wealth of information provided by three-dimensional raster scanning. State-of-the-art methods for computational analysis of ophthalmic imaging data have recently been reviewed in Progress in Retinal and Eye Research (Kanagasingam et al., 2014). Current advances in computational image analysis are not only able to predict visual function based on OCT assessments (Bogunovic et al., 2015) and provide precise risk assessments for disease progression (de Sisternes et al., 2014), but are also capable to predict the future disease course of patients under therapy with very high accuracy (Vogl et al., 2015). However, advanced computational pre-processing techniques such as motion artefact removal and registration are required (Montuoro et al., 2014; Wu et al., 2014a). Obviously, a precise automated quantification of the relevant retinal morphologic lesions is necessary, but currently only achieved for few morphologic factors (Garvin et al., 2009; Schlegl et al., 2015; Xu et al., 2015b; Zhang et al., 2012; Zhang et al., 2014). Computational disease modelling based on longitudinal OCT data will undoubtedly aid the development of personalized therapeutic approaches on a population level, and introduce higher levels of efficacy, safety and cost effectiveness into modern anti-VEGF therapy.

7.2. Novel biomarkers from future diagnostic modalities

The therapeutic efficacy of VEGF inhibition in combination with the potential of OCT-based quantitative biomarkers to guide individualized treatment may shift the medical need from CNV treatment towards other and/or additional treatment modalities. Future therapeutic approaches will likely focus on early and/or disease-modifying interventions aiming to protect the functional and structural integrity of the morphologic complex that is primarily affected in AMD, i.e. the choriocapillary – RPE – photoreceptor unit. Obviously, new biomarkers tailored towards early detection of the specific changes in this functional unit will be required as well as follow-up features defining the optimal therapeutic goal during extended therapy, i.e. life-long in neovascular AMD. Three novel additions to the OCT armamentarium are particularly promising in their capability to identify the biomarkers of the future:

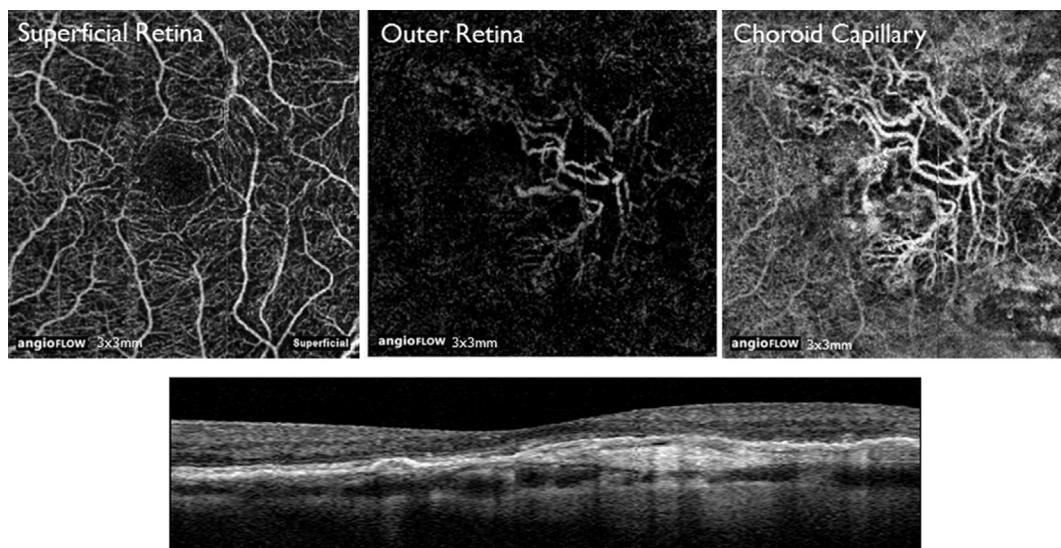


Fig. 10. OCT angiography, a novel dye-less imaging method, enables visualization of blood flow in the retinal and choroidal vasculature. This 77-year old patient had previously received 17 anti-VEGF injections. Conventional OCT shows a dry retina and a fibrovascular pigment-epithelial detachment. OCT angiography reveals the inactive choroidal neovascular net within the pigment-epithelial detachment, characterized by mature, tangled vessels appearing in an organized fashion. Courtesy of Andreas Pollreisz, MD.

7.2.1. Polarization-sensitive OCT

Polarization-sensitive OCT is able to provide intrinsic tissue-specific contrast based on light–tissue interactions and depolarizing properties of the examined structures. The methodology used in polarization-sensitive OCT and its manifold clinical applications have been reviewed in Progress in Retinal and Eye Research by Pircher et al. (2011). In AMD (Fig. 9), this technology can selectively visualize the RPE layer based on its intracellular pigment granule content, including melanolysosomes and melanolipofuscin (Baumann et al., 2012). Thus, the specific patterns of RPE plasticity including RPE atrophy, hypertrophy, and migration can be assessed and quantified (Roberts et al., submitted). Moreover, polarization-sensitive OCT allows precise quantification of RPE-driven disease at the early stage of drusen, highlighting the pathognomonic conversion towards advance atrophic or neovascular AMD (Schlanitz et al., 2011). This is decisive in differentiating between the individual CNV lesion types in early stages by delineating the RPE layer localization compared to the neovascular complex (Ahlers et al., 2010).

Drusen dynamics including growth and regression are fundamentally relevant in the progression of early towards late AMD, regardless of whether the progression path leads to geographic atrophy or choroidal neovascularization (Ouyang et al., 2013; Yehoshua et al., 2011). RPE-related changes of the choriocapillary – RPE – photoreceptor complex such as RPE thickening or mottling overlying drusen, or outer retinal vortexing may be important signs in the progression of AMD (Wu et al., 2014b). As focal microenvironmental inflammatory changes have been implicated in the pathogenesis of geographic atrophy and CNV (Zhu et al., 2009), such biomarkers may be relevant outcome measures in future targeted therapy.

7.2.2. OCT angiography

The novel technology of OCT angiography enables non-invasive dye-free visualization of the retinal and choroidal vasculature. The extensive Progress in Retinal and Eye Research review by Leitgeb et al. (2014) provides a comprehensive overview of methodology and applications. In neovascular AMD (Fig. 10), OCT angiography is capable of visualizing the neovascular net directly with more precision as it is unhindered by FA masking effects and in its three-dimensional location due to the 3D talents of raster OCT (Moult et al., 2014). In addition to the proliferative neovascular net, changes indicating malperfusion within the adjacent choriocapillary bed can be noted. These *in-vivo* OCT features are consistent with histological findings indicating loss of physiological choriocapillaries before reactive proliferation of choriocapillary neovessels likely induced by expression of VEGF in the overlying compromised RPE (Bhutto and Lutty, 2012). Angiographic OCT with its potential to capture choriocapillary, RPE, and neuroretinal features provides novel types of biomarkers identifying disease pathophysiology rather than late consecutive features during advanced neovascular AMD. Assessment of the choriocapillary layer and its changes associated with drusen may provide important insight into the pathophysiologic development of AMD, in which involvement of the choriocapillary has been demonstrated (McLeod et al., 2009; Mullins et al., 2014; Whitmore et al., 2015).

Moreover, blood flow in neovascular tissue may be measured and monitored during therapy (Dansingani et al., 2015; Jia et al., 2014). In the future, patients may be retreated based on the recurrence of flow in CNV lesions before the development of fluid exudation within neurosensory layers of the retina. OCT angiography may be used to judge the precise morphological configuration of the neovascular net in AMD, as well as differentiating between the sea-fan pattern of an actively leaking CNV and the appearance of a mature neovascular membrane (Fig. 10). While

aggressive therapy is indicated for leaky membranes, mature CNV membranes may in fact have a protective role in maintaining RPE nourishment. Obviously, such supportive mature neovascularization is not a useful biological target for therapy; rather, an accurate balance is required between VEGF inhibition and maintaining the necessary physiological levels of VEGF in the retina. This is even more relevant in combination therapies including other growth factors as targets. As outlined above based on data from CATT, IVAN, and HARBOR, antiangiogenic therapy if given intensively and continuously may lead to regression of the CNV lesion, but will also be associated with progressive RPE atrophy and development of atrophic scars as a consequence of permanent VEGF inhibition (Channa et al., 2015). The fact that SRF is protective against the development of GA may likely suggest that the presence of a perfused subretinal CNV provides oxygen and nutrients to adjacent RPE and photoreceptors, while pharmacologic occlusion of the subretinal net leads to retinal atrophy. Angiographic OCT is a most impressive example for a profound change in disease understanding and management driven by advances in diagnostic technology.

7.2.3. Adaptive optics imaging

Retinal imaging employing adaptive optics technology substantially increases the transversal resolution of OCT and scanning laser ophthalmoscopy, and is capable of resolving individual RPE and photoreceptor cells (Felberer et al., 2014; Zarbin, 2004). However, due to the complex and destructive anatomical circumstances in neovascular AMD, the application of adaptive optics imaging has thus far been limited mainly to non-neovascular AMD (Rossi et al., 2013; Zayit-Soudry et al., 2013), and will require some technical maturation before being able to provide a useful management tool in neovascular AMD. Nevertheless, this modality is particularly appropriate to highlight early features during the pathophysiological development of neovascular AMD. Subretinal drusenoid deposits for instance show a significant correlation with the development of CNV (Roberts et al., submitted, Hogg et al., 2014). Findings from studies using adaptive optics implied that decreased photoreceptor function in early AMD may be possible, suggesting that eyes with pseudodrusen appearance may experience decreased retinal (particularly scotopic) function in AMD independent of CNV or RPE atrophy (Mrejen et al., 2014; Steinberg et al., 2015). Adaptive optics OCT with its superior axial and transversal focus will provide in depth insight into the photoreceptor role of AMD development, both atrophic and neovascular. Similarly, adaptive optics technology may be able to contribute significantly to our understanding of the pathophysiology of CNV development. Given its ability to image individual cells, it may provide a key diagnostic tool in the evaluation of the photoreceptor – RPE – choriocapillary unit, and may in combination with polarization-sensitive OCT and OCT angiography help to unveil the complex mechanisms of disease in AMD in the future.

7.3. Conclusion

In conclusion, the future of neovascular AMD diagnostic evaluation and guided management has just begun with the identification of sensitive and robust OCT-based imaging biomarkers for individualized prognosis in CNV disease and antiangiogenic therapy. Multimodal innovative imaging technologies, such as PS-OCT, OCT angiography, and adaptive optics allow access to yet unidentified biomarkers representing the origin of neovascular AMD as well as functionally relevant therapeutic aims. Improved big-data applicability and reproducibility aided by computerized OCT analysis will likely allow personalized antiangiogenic therapy with minimal interventions, while providing maximum disease control,

using advanced imaging software and hardware. It is the responsibility of the scientific and clinical community to follow the open path of advanced imaging in a collaborative and interdisciplinary approach together with ophthalmologists, biologists, physicists, and computer scientists in an efficient interdisciplinary approach.

Conflict of interest

No conflict of interest exists for any author.

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