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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,