

# A Decade of Anti-VEGF Drugs in Ophthalmology- Successes and Challenges

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## Abstract

The discovery of anti-VEGF drugs has revolutionized the management of age-related macular degeneration, diabetic macular oedema and retinal vein occlusion. This paper discusses how the management evolved in the anti-VEGF era, addresses salient yet unresolved aspects of early identification and monitoring but also takes notice of challenges associated with long term care. The paper proposes to increase the role of patient self-management, as this has been shown to be effective in many other chronic clinical conditions, and sets out the requirements making self-management operational.

**Keywords:** Anti-VEGF treatment; Age-related macular degeneration; Diabetic macular oedema; Retinal vein occlusion; Patient self-management; Disease management

## Background

The discovery of anti-VEGF drugs has revolutionized the management of age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal vein occlusion (RVO). We look back to almost ten years of anti-VEGF experience in ophthalmology and remain very optimistic about the therapeutic yield in medical conditions that, before the anti-VEGF era, had a poor long-term prognosis [1-10]. At those times, where photodynamic therapy in combination with verteporfin was the only principled approach in AMD management, ophthalmologists had usually bad news for their patients and actually accompanied them to the state of complete loss of central vision.

Today patients are promised a clear treatment response if anti-VEGF medications are provided timely. A network meta-analysis, comparing the two currently licensed drugs Ranibizumab (Lucentis<sup>®</sup>) and Aflibercept (Eylea<sup>®</sup>) against placebo, showed that the benefits for all relevant efficacy outcomes were consistently positive [11]. A Cochrane systematic review agreed with these findings [12]. Moreover, in a modelling exercise based on epidemiologic data from the United States, Bressler and co-workers found that monthly ranibizumab treatment would reduce the incidence of loss of vision by 37 percent and the incidence of legal blindness by 72 percent within two years [13]. Bloch and co-workers, assessing the Membership register of the Danish Association of the Blind, found that the incidence rate of legal blindness attributable to AMD in citizens aged  $\geq 50$  years decreased by 50% between 2000 and 2010, the bulk of the reduction occurring after 2006, when anti-VEGF drugs were broadly introduced [14].

However, despite this good news, several problems regarding the management of AMD, DME and RVO prevail. First, even cautious estimates state that under-treatment remains a huge problem. Under-

treatment may have several reasons. Among them, non-ophthalmologic caregivers lack the awareness for early wet AMD but also public awareness for AMD and the risk of blindness remains low [15]. Also, the perceived financial burden of this treatment for the health budget [16] may often drive politicians, patients an even general ophthalmologists to remain hesitant whether to start and more importantly, whether to maintain the long term efforts for such a treatment [17]. Hence, outcome data with the highest level of evidence is needed to encourage the fight against blindness in the elderly population [11,12].

## Challenges of Clinical Management

### Early identification and monitoring

The Amsler grid, introduced in 1947 [18], is the most commonly used screening instrument for metamorphopsia in clinical practice. Over the 65 years since the introduction of this simple and commonly used test, there have been discussions about its clinical usefulness and practicability. Crossland and Rubin found various obstacles such as difficulty with fixation in self-monitoring experiments or the phenomenon of perceptual completion, leading to high number so false negative results [19]. It also has been argued that Amsler grid testing is difficult to perform correctly and thus often leads to ambiguous test results. Fine and colleagues recognized that the screening with an Amsler grid is not fully self-explanatory [20]. In addition they found that only about ten percent of patients spontaneously complained about a distorted vision when using the Amsler grid on their own.

In 2012, Mathew and Sivaprasad introduced the concept of "environmental Amsler" defined as: the perception of visual deterioration or distortion of objects in everyday life [21]. By asking patients whether they believed that disease had reactivated, they showed that the "environmental Amsler grid" was well correlated with Optical Coherence Tomography (OCT) findings, drop of visual acuity

and other clinical findings requiring re-treatment. They concluded that the “environmental Amsler” could be a promising method of patient self-monitoring in a selected group of patients.

In a recent meta-analysis of diagnostic accuracy studies [22] the average sensitivity of the Amsler grid was 0.78 percent (95% confidence intervals; 0.64-0.87) and the pooled specificity was 0.97 percent (95% confidence intervals; 0.91-0.99) thus bearing a good potential to rule-out AMD in the screening setting. This is important and reassuring, as outside retinal subspecialty centres, the Amsler grid remains the most often used screening test for macular disease [23].

The meta-analysis also looked at new technologies that have recently become available: the PHP home measurement device ForeseeHome® (Notal Vision Ltd, Tel Aviv, Israel) by Loewenstein [24], [25], and a Vernier acuity task that has been programmed into a smartphone app [26]. The pooled sensitivity and specificity of studies assessing the PHP were slightly higher than for the Amsler grid, but some authors highlighted disadvantages particularly in terms of user friendliness and complexity of the task. These new developments point at the direction in which screening and monitoring of patients with early stages of AMD should go [27]. For patients with macular disease, mobile devices can indeed play an important role to improve timely care of retinal damage [22].

To date, a self-monitoring approach for healthy subjects bearing an increased risk to develop AMD has not been established. For patients receiving anti-VEGF treatment, an OCT based management is considered as gold standard. Self-measurement approaches both for patients currently receiving treatment and for patients with dry AMD with a risk for relapse bear a great potential to improve disease monitoring. Broad availability of self-monitoring would have considerable impact on the delivery of care and on the patient-doctor interaction also.

### Long term care of AMD

Almost ten years of anti-VEGF treatment in AMD revealed some challenges in clinical management that were not visible in the early times. In the SEVEN-UP study reporting the 7-year outcomes of patients with wet AMD receiving ranibizumab treatment, a considerable amount of patients had lost the visual gains made in the first years of treatment at the end of the 7th year [28]. Whether this relates to the natural course of the disease or to the occurrence of tachyphylaxis or tolerance to treatment associated with long-term intravitreal drug use is not yet fully understood [29-31].

With the FDA approval of the second anti-VEGF drug, aflibercept (Eylea®) in the US in 2011 started a discussion about the usefulness of therapy switches in case of tachyphylaxis. Evidence regarding the clinical usefulness are still sparse. In a recent study, Batioglu and colleagues [31] showed a short term benefit of switches from ranibizumab to aflibercept in 28 patients investigated. However, to what extent these findings translate to clinical practice at large and whether the same effects occur in switches from aflibercept to ranibizumab need further exploration.

Another problem of patient management is therapy adherence. In a recent study, a French group published five-year data about the adherence to ranibizumab in a real-life setting [32]. Of 201 patients, more than half had discontinued treatment after five years. Those 58 patients who completed the questionnaire despite discontinuing the anti-VEGF treatment claimed as main reason for discontinuation the long travel distance from home to hospital, subjective dissatisfaction

with the benefits of intravitreal injections, and the excessive burden of periodic follow-up visits.

### Quality assurance

Establishing a standardized clinical set-up and monitoring for the management of AMD, DME and RVO remains a key asset [15]. Software solutions helping to track individual patients and collecting outcome data are of great importance. Evidence suggests that for an optimal treatment caregivers need to adhere to stringent treatment protocols [16]. Particularly since patients’ adherence is an important issue in the management [32], caregivers need to act as pacemakers for the delivery of care. Further research should increase our understanding about the patient burden and costs associated with the regular visits. More insights into this could help optimizing the management and could eventually improve patients’ adherence.

### Outlook

We believe that sophisticated, but easy-to-use screening and monitoring devices in the hand of the patients will have a great impact on timely interventions and patients’ long term adherence to treatment. As in many other chronic clinical conditions, patient self-management bears a great potential [33]. Particularly in intervals without treatment self-monitoring could help avoiding unnecessary delays of re-treatment. Caregivers need to acknowledge that AMD, DME and CRO need to be managed in highly structured and standardized settings as treatment delays or insufficient treatment may lead to irreversible vision loss.

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