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EDITORIAL

15 years of anti-VEGF treatment for nAMD: success or failure or something in between?

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Some 8.1 million people suffer from visual impairment due to neovascular age-related macular degeneration (nAMD) [1]. The main therapeutic target is vascular endothelial growth factor (VEGF), which promotes angiogenesis and vascular permeability; key features of the pathophysiology of nAMD. Biologicals that inhibit VEGF (Lucentis, approved in 2006, Eylea in 2011, Beovu in 2019, and Avastin, used off-label) cause rapid functional improvement and normalization of macular morphology with reductions in intra- and subretinal fluid, hyperreflective material and pigment epithelial detachments. However, despite blockade of VEGF, the neovascular complexes continue to expand—a finding that is hardly surprising given the complex nature of the disease [2].

Since their approval 15 years ago, anti-VEGF therapies have reduced the rates of visual impairment or blindness due to nAMD [3]. However, data from routine care has revealed that the visual gains seen at 1 and 2 years are lost over time. While this is in part due to sub-optimal management [4], progression to atrophy and/or fibrosis can occur despite optimal VEGF therapy [5, 6]. We consider below some of the reasons for such loss of vision gain.

First, maintaining the initial functional and morphological gains requires constant monitoring and prompt re-treatment, which impose a huge burden on service providers, patients and carers. Even short delays in re-treatment can cause irreversible vision loss [7]. Limited resources in some health care systems impose delays in re-treatment [8]. Patient non-compliance due to costs, fatigue or simply a perception of treatment failure, are also reasons for cessation of treatment in the long run [9].

Second, delays in diagnosis and treatment initiation can result in permanent morphological damage limiting potential future functional gains [8, 10].

Third, although undertreatment [4] remains a consistent finding in long term follow up cohorts of previously completed clinical trials [11–13] and real-world data [14], evidence shows that anti-VEGF treatments do not modify the underlying disease, and patients show progression to atrophy even under optimal therapy [13]. Atrophy of the RPE and outer retinal layers is a common finding, exhibited by three quarters of all eyes followed up for 7 years [13]. The mechanisms leading to atrophy remain to a large extent unexplained. Early studies suggested that VEGF inhibition itself might promote atrophy [2, 6], however others did not find a correlation between atrophy and treatment frequency [15, 16].

Fourth, progression to fibrosis that results in the disorganization of photoreceptors, RPE, Bruch's membrane and choriocapillaris is another important cause of visual morbidity in treated nAMD. Long term follow up of participants of large trials found that half of all study eyes had evidence of fibrosis 5 to 7 years after enrolment [13, 17]. Defining fibrosis as an outcome in clinical trials is challenging for many reasons: the molecular mechanisms leading to fibrosis are poorly understood, there are no good animal models, there is a lack of consensus in defining fibrosis in the clinical setting and no agreement on the optimal imaging biomarkers for this feature. Subretinal hyperreflective material (SHRM), an OCT feature of nAMD, is a predictor of fibrosis [5, 18] that is considered its proxy. However with treatment SHRM can disappear, persist or increase [19], emphasizing the need for better characterization of this biomarker in terms of fibrosis composition, severity and extent.

WHAT ARE THE SOLUTIONS?

Longer acting, more durable therapies

Fewer treatments impose less burden on service providers and patients, which may translate into better outcomes. The initial studies were performed some 15 years ago with anti-VEGF biologicals administered monthly. Although studies using less burdensome treatment regimens such as the pro re nata and treat and extend approaches result in visual gain in the short term, much of this gain can be lost over time [20]. There have been recent developments in durability through use of extended release systems (SUSVIMO [21]) and new drugs like BeoVu [22], but the former requires invasive surgery to implant a device into the vitreous cavity and the latter has been found to have an unacceptable safety profile with a risk of inflammation induced retinal vascular occlusions [23]. Nonetheless these recent entries also rely on the same mechanism of action (i.e., VEGF inhibition), therefore unlikely to reduce the morbidity over the longer term arising from progression of the disease to atrophy and fibrosis.

Therapies with novel MoA

Vabysmo, recently approved, has a dual mechanism of action simultaneously targeting VEGF and angiopoietin-2 [24]. Blockade of these two main drivers of angiogenesis might be more effective in preventing expansion of the neovascular complexes and thus recurrence of disease activity. The demonstration of even limited efficacy by pegcetacoplan in preventing expansion of geographic atrophy (GA), the other late manifestation of AMD, through complement inhibition also raises the possibility of combining therapeutics in modulating the progression to atrophy in patients with nAMD [25].

New approaches to prevent atrophy and fibrosis

Besides angiogenesis and vascular instability there are other pathways involved in the development and progression of AMD, including dysregulation of the immune system, inflammation, oxidative stress, neurodegeneration, and even alterations in the gut microbiota [26]. These pathways offer additional targets for therapy and combined with VEGF inhibition have the potential to provide enhanced outcomes.

Earlier intervention

Prior trials have shown that in intermediate AMD antioxidant supplementation reduces progression to nAMD but not GA [27].

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The demonstration that complement inhibition can reduce the growth of GA has led to speculation that immunomodulation may be protective against atrophy. Intervening at the stage of intermediate AMD also poses its own challenges, as progression to advanced disease usually requires large studies over many years.

The road to success is paved with failure (Thomas Edison)

Despite the challenges that AMD still represents 15 years after the introduction of the first therapy, the current pipeline looks as diverse and comprehensive as never before. Increased knowledge in AMD pathophysiology and novel strategies and clinical trial designs offer hope for a bright future.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to the intellectual content of the submission. The corresponding author confirms that Dr B Armendariz and Dr S Fauser co-wrote this paper. The corresponding author confirms responsibility for the decision to submit the paper for publication.

COMPETING INTERESTS

UC was visiting Professor at Hoffmann La Roche who hold a license for anti-VEGF treatments which are commented on in this perspective. Professor UC no longer holds this position as her term has ceased. Dr BGA and Dr SF are employees of Hoffmann La Roche.

ADDITIONAL INFORMATION

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