Undertreatment of Neovascular Age-Related Macular Degeneration after 10 Years of Anti-Vascular Endothelial Growth Factor Therapy in the Real World: The Need for A Change of Mindset

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Keywords

Anti-VEGF · Neovascular age-related macular degeneration · Treatment burden · Undertreatment

Abstract

Purpose: To assess the gap between visual acuity (VA) outcomes with anti-vascular endothelial growth factor (anti-VEGF) therapies in clinical trials and real-world practice, and explore the reasons for this gap. **Methods:** The literature was searched from January 1, 2013, to June 30, 2018, for studies reporting VA gains and injection frequencies in clinical trials and real-world practice. **Results:** Clinical trials of anti-VEGF agents and their extension studies demonstrated initial VA gains maintained at 4 years and beyond (up to 7 years) with continuous proactive treatment. Visual outcomes correlated with injection frequency. In real-world practice, patients are usually undertreated, accounting for the VA decline over time. Reasons for undertreatment include the burden of in-

jections and monitoring visits imposed on patients/caregivers. However, another primary reason is the general mindset in the ophthalmological community that sustained benefits with treatment are not possible, leading to poor compliance and creating a vicious circle. **Conclusions:** Initial VA gains can be maintained with more intensive/proactive approaches. Promising new treatments requiring less frequent injections/monitoring will help in the near future; meanwhile, better results could be achieved by changing the community mindset that contributes to undertreatment.

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Introduction

As improved healthcare extends life expectancy, it is estimated that by 2040 the number of individuals in Europe with late-onset age-related macular degeneration (AMD), including geographic atrophy and choroidal

neovascularization, will range between 3.9 and 4.8 million [1]. In the USA, this number is projected to increase from 1.7 million in 2010 to 3.8 million by 2050 [2]. Such a surge in prevalence represents a major challenge for healthcare providers who must meet the logistical and economic burden of providing adequate treatment to all AMD patients [3].

The use of anti-vascular endothelial growth factor (anti-VEGF) therapies, more particularly anti-VEGF-A, has introduced a paradigm shift in the treatment of neovascular AMD (nAMD) [4–6]. Results from pivotal trials of ranibizumab and aflibercept, the anti-VEGF therapies approved for the treatment of nAMD, have demonstrated their efficacy in improving visual acuity (VA) [7–9]. Bevacizumab is another anti-VEGF agent used unlicensed for the treatment of nAMD [10–14].

Questions have been raised, however, as to whether anti-VEGF therapy achieves similar outcomes in clinical practice. A literature review was carried out for the period from 1 January 2013 until 30 June 2018 using key terms (treatment burden OR undertreatment OR suboptimal management OR suboptimal treatment) AND (nAMD OR neovascular age-related degeneration OR wet AMD) to identify to what extent clinical trial outcomes with ranibizumab and aflibercept in nAMD reflect those achieved in the real world, and the reasons for the gap between clinical trials and real-world results. Based on this evidence, some answers to the following questions are proposed: are patients generally sufficiently treated and what are the reasons for undertreatment?

Clinical Trial Result Overview

Without treatment, patients may lose up to 4 lines of VA within 2 years of the nAMD diagnosis, and more than 40% of patients may lose at least 6 lines within 3 years [15]. In contrast, after 2 years of monthly treatment with ranibizumab (0.5 mg), patients experienced a mean best corrected VA (BCVA) change of +6.6 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the MARINA study and +10.7 letters in the ANCHOR study [7, 8]. The regimen that first proved its efficacy consisted of once-monthly intravitreal injections of ranibizumab (0.5 mg) [7]. After MARINA and ANCHOR, attempts were made to reduce the number of injections and individualize treatment in the HARBOR study, and thereby a balance between injection frequency and optimal vision gain was found [16, 17].

Results from the VIEW studies indicated that aflibercept and ranibizumab were equally effective in improving

BCVA and preventing a BCVA loss at 96 weeks (similar proportion of patients maintained vision at week 52), with equivalent benefits provided by aflibercept every 4 weeks versus 3 monthly loading injections followed by aflibercept every 8 weeks [9, 18]. There was a trend towards lower VA gains in the second year versus the first, likely due to the fact that in the second year a capped pro re nata (PRN) approach was followed which resulted in fewer injections (4 injections on average during weeks 52–96).

The PRN regimen indeed requires fewer injections, but the burden of monthly monitoring visits remains unaddressed. Furthermore, PRN is a reactive regimen that uses disease recurrence as the primary retreatment parameter [11]. A treat-and-extend (T&E) regimen has also been investigated to treat active lesions proactively, while minimizing clinic visit and injection frequencies, by allowing extension of injection intervals [19–21]. Once the maximum VA is achieved and there are no signs of disease activity, the treatment intervals are extended stepwise until signs of disease activity or visual impairment recur.

Extension Studies

The number of injections were also decreased in the extended follow-up of randomized control trials (HORIZON [22], SEVEN-UP [23], SECURE [24], CATT follow-up [25], and VIEW1 extension [26]), which mostly followed a PRN regimen, with the number of injections per year ranging from 1.6 to 6.1 [27].

In most trials, gains from baseline were still maintained at year 4 (ranging from +1.7 to +7.1) [27]. At year 5, however, the VA declined to below-baseline levels in HORIZON and in the CATT follow-up (−0.1 and −3.3) [27]. Assessment of treatment frequency in the CATT study revealed that the 71% of nAMD patients who had a follow-up of 5.5 years only received 4.8 injections in year 3, 4.5 injections in year 4, and 4.0 injections in year 5 [25].

A possible reason why these studies showed a decrease in vision in the long term could be the allowance of fluid recurrence with PRN dosing and subsequent underdosing [14, 25, 27]. In line with this hypothesis, in studies that used a more consistent dosing, VA was largely maintained in the long term [27]. The greatest long-term gains (+12.1 at 7 years) were achieved in a study that kept patients on a continuous fixed-interval dosing (every 4–8 weeks) of anti-VEGF therapy; as such, the study had the highest mean number of injections/year (i.e., 10.5) [28].

Overall, the mean number of injections during the extension studies was positively correlated with the average VA gain from baseline (Pearson's correlation: 0.91) [27].

Real-World Outcomes

The key question remains as to how many injections patients receive in real-world practice, and what the associated VA gains are. It is well-recognized that the behavior during clinical trials, characterized by limited inclusion and exclusion criteria, a higher level of motivation, and regular follow-up, cannot be replicated in the real world. Most importantly, trials are of a finite duration whereas nAMD is a chronic disease requiring ongoing injections to maintain the visual outcomes achieved in early therapy. The monthly dosing for ranibizumab has often proved to be impractical in real-world practice [29]. As a result, there has been a shift toward the more flexible regimens including PRN and later T&E, although gains achieved in clinical trials with PRN have not been as high [11, 21], and PRN still requires monthly monitoring visits, which in routine practice are not feasible for most elderly patients.

Short Term

The visual gains achieved in real-world practice are not as impressive as those achieved in clinical trials, even in the short term [30]. The UK AMD EMR Users Group, which assessed 92,976 ranibizumab injections in 12,951 eyes followed for at least 3 years, found VA gains for eyes predominantly treated using a PRN retreatment approach of +2, +1, and -2 ETDRS letters at 1, 2, and 3 years, respectively; the mean number of injections was 5.7 in year 1 and 3.7 in years 2 and 3 [26].

In a large retrospective US real-world dataset including 3,350 ranibizumab and 4,300 aflibercept treatment-naïve eyes, ranibizumab and aflibercept yielded comparable visual outcomes with similar injection patterns over 12 months [31]. The mean change from the index (i.e., the first injection date) in VA letter scores was -0.30 for ranibizumab and -0.19 for aflibercept and the mean number of injections was 6.7 and 7.0, respectively.

With an adequate treatment schedule, however, maintaining VA gains in real-world practice is not impossible. In particular, the T&E regimen seems to yield better visual outcomes compared to the PRN approach. A meta-analysis of real-world studies of ranibizumab (42 global studies including over 26,000 patients) showed mean VA changes of +8.8, +6.7, and +5.4 ETDRS letters in studies with the T&E regimen versus +3.5, +1.3, and -1.9 letters, respectively, in studies with the PRN regimen at 1, 2, and ≥3 years, respectively; T&E patients received more mean injections per year (6.9 vs. 4.7, $p < 0.001$) but had fewer mean visits (7.6 vs. 8.8, $p < 0.001$) [32].

Data was analyzed for a cohort of 1,198 treatment-naïve eyes that followed a T&E regimen, mostly with ranibizumab from the Fight Retinal Blindness (FRB) registry, which tracked the outcomes of anti-VEGF treatment for nAMD in Australia, New Zealand, and Switzerland. It was observed that patients had a +5.3 logMAR letter gain at 24 months, with an overall mean of 13 injections (7.5 in the first year and 5.5 in the second) and a mean number of visits of 7.5 and 6.7 in the first and second year, respectively, suggesting that eyes managed by a T&E regimen in clinical practice could achieve a good visual outcome, at least in the short term [30, 33].

Long Term

Optimal visual outcomes are more challenging to achieve in the long term (≥5 years) in real-world practice [30]. In a 5-year analysis of real-life VA gains and injection patterns in 1,083 patients with nAMD undergoing PRN treatment, it was observed that the initial VA gain was not maintained at 5 years [34]. By year 5, while 10% of the patients had gained >15 letters, 56% had remained stable and 34% had experienced a VA loss of >15 letters. The median injection frequency was 6 in year 1 and between 4 and 5 in subsequent years.

Analyses of the long-term outcomes of 1,212 eyes (baseline VA: 55.1; 18.8 letters) treated with anti-VEGF, predominantly ranibizumab, for at least 5 years from the FRB registry showed that the maximum VA gains from baseline were observed at 6 months (6.3 letters), with VA returning to baseline levels by 5 years in the 549 eyes followed (+0.7 letters) and to below baseline levels by 7 years for the 131 eyes still followed (-2.7 letters) [35]. The median number of injections was 6 in the first year and 5 per year thereafter. This outcome is still better than the outcome from the SEVEN-UP extension study in which participants of ANCHOR/MARINA, then HORIZON, were subsequently treated in routine clinical practice and reported a mean loss of 8.6 letters over 7 years [23]. The lower number of injections in SEVEN-UP [23] is likely to account for reduced long-term visual outcomes compared to observations from the FRB registry [35].

Another important aspect synonymous with long-term follow-up of patients treated with anti-VEGF is the risk of fibrosis and macular atrophy as discussed in the SEVEN-UP extension study and the FRB registry. A total of 61% of the patients developed submacular fibrosis, which might be an indicator of undertreatment, and 98% of the patients developed macular atrophy which was considered a primary reason for vision loss in the SEVEN-UP extension study [23]. However, in FRB, 31% of

the patients developed subretinal fibrosis and only 37% of the eyes developed atrophy resulting in a loss ≥ 10 [35]. These results suggest that the vision loss in long-term anti-VEGF treatment are governed by multiple factors, among which undertreatment remains one of the key drivers.

Overall, these results suggest that a low intensity of treatment in real-world practice is one of the main factors accounting for the gradual decline in VA in the long term despite anti-VEGF therapy. A low baseline VA possibly due to a delay in diagnosis and treatment initiation and the presence of preexisting conditions (scars) could also contribute to poor outcomes in the real-world scenario. These findings are supported by other real-world studies showing a decline in hospital visits and the number of injections over time [36–39].

In summary, as shown in clinical trials, sustained high gains at 7 years are possible with more intense regimens (up to +12.1 letters with a mean of 10.5 injections/year) [28], but no such regimen and therefore no such gains have been observed in the real world due to a reduction of the injection frequency over time. Long-term follow-up data are not yet available for aflibercept, which entered the market later than ranibizumab.

Key Factors Responsible for Undertreatment

Patient Perspective

Patient adherence (defined as the extent to which patients attend their monitoring and injection visits) and persistence (which measures the time from treatment initiation to discontinuation) appear to pose significant challenges in clinical practice, as observed in various real-world studies in nAMD patients as described below.

In a French study, fewer than 40% of the 551 patients studied received the recommended initial 3 monthly injections of ranibizumab, and not a single patient was assessed every month [40]. In a Swedish study, 21% of the 471 patients treated with ranibizumab had discontinued treatment before 1 year [41]. Similarly, low persistence rates are reported in the real world (84% at 12 months and 63% after 2 years) compared with prospective trials (91–92% and 83–85%, respectively) [37]. It should be noted that these low rates were observed in Australia, which delivers the earliest and most optimized treatment compared to other countries [32].

Low adherence and persistence can have major consequences for visual outcomes. It was observed in an Australian study that, of 115 eyes for which anti-VEGF treat-

ment had been discontinued for more than 3 months, 91% developed reactivation of choroidal neovascular lesions and a significant decline in VA [38].

The factors affecting adherence from the patient's perspective were the psychosocial burden, the time burden, and the VA benefits expected [42]. A systematic review revealed that the anticipated discomfort is often greater than the actual discomfort experienced during intravitreal injections, and the reasons for patient apprehension include the thought of having an injection, fear of losing eyesight, and fear of the unknown [43]. An Australian study based on semi-structured interviews of 40 patients revealed the psychosocial impact of repeated intravitreal anti-VEGF injections; anxiety was most common, related not just to treatment but also to factors such as fear of losing eyesight and unfamiliarity with the treatment procedure. Many patients were restricted to sedentary activities after the injection, owing to treatment side-effects. Also, patients were accepting of treatment costs but not of travel-related costs; travel for treatment also placed a burden on caregivers [42]. In another Australian study, the drop-out rate over a 2-year period was observed to be significantly higher (50 vs 28%, $p = 0.002$) in patients living ≥ 100 km from the clinic ($n = 68$) than in those living < 100 km ($n = 182$) [44]. Similarly, in a French study, the distance between home and hospital and the need for regular follow-up visits were listed among the reasons for treatment discontinuation (Fig. 1) [45].

The significant time burden associated with both treatment and monitoring visits, for both patients and caregivers, also appears to have a significant impact on treatment adherence. In a US study of 75 nAMD patients and 13 caregivers [46], it was reported that the average time per visit was almost 12 h, including pre-appointment preparation, travel, waiting time, treatment time, and post-appointment recovery. Caregivers had to take time away from work and personal activities to accompany patients.

However, patients perceive treatment to be a necessity and are willing to tolerate it if positive visual outcomes can be expected [42]. In a German survey of 284 patients, the factor influencing treatment options in the majority (73.6%) of the patients was “change in VA” [47]. Patients were also willing to accept an additional time spent per physician visit of 21.2 hours (including waiting, treatment, and traveling time) for VA improvement. A questionnaire-based survey of 200 patients suggests that most patients were ready to accept a monthly regimen to prevent recurrent disease activity [48]. In another German study, 39% of the 19% (18/95) patients who discontinued

Fig. 1. Reasons for discontinuation as assessed in a 5-year real-world study in France. Answers are based on a 7-item questionnaire completed by phone or e-mail by 58 patients receiving ranibizumab treatment. IVT, intravitreal. Reproduced from Boulanger-Scemama et al. [45]. Copyright © 2015, published by Elsevier Masson SAS. All rights reserved.

treatment after 96 weeks of PRN anti-VEGF treatment did so due to subjective dissatisfaction with the benefit; 62.1% were afraid of a negative examination result, whereas 1 in 5 were afraid of intravitreal injections [49].

Another important aspect to consider is the lack of non-standardized patient-centered outcome measurements. A working group supported by International Consortium for Health Outcomes Measurement (ICHOM) recommended that the potential outcomes be identified through a review of outcomes collected by existing registries and reported in major clinical trials [50]. Some of the outcomes recommended to be recorded were distance VA readings (in the LogMAR scale), disease control, quality of life, and disutility of care. The standardized outcome set might help physicians to make decisions regarding treatment and performance, patients to make well-informed choices about their treatment, and insurers to understand the value of care that is being funded [50].

Overall, the burden of frequent injections, monitoring visits, and associated time constraints may thus act in synergy with any perceived/expected lack of efficacy to contribute to poor compliance and a decline in VA over time. Better awareness among patients that their disease is chronic and will require prolonged therapy in order for the vision to be maintained has actually been shown to contribute to better adherence and persistence over a 12-month period. At the end of 6 and 12 months, the percentage of patients adherent to treatment was 97 and 93%,

respectively, among patients in an educational program versus 83 and 74%, respectively, among those not in an educational program [51].

Clinic and Physician Perspective

The management of nAMD with currently licensed therapies also places a significant logistical burden on clinics and physicians [52].

Monitoring visits are actually the most time- and resource-consuming part of patient care and one of the main issues for physicians treating nAMD, often making monthly regimens unachievable in clinical practice [29, 53]. In that respect, it should be noted that the T&E approach, typically associated with higher VA gains than PRN as indicated above, remains demanding in terms of visit frequency. Not only does it require more injections than PRN, but also some clinics do not have a time-system to transmit optical coherence tomography images to physicians; as a result, they have to separate injection visits from monitoring visits, adding to the treatment burden.

The physicians' perspective is illustrated well by the 2018 ASRS Preferences and Trends (PAT) membership survey which involved 1,029 retina specialists around the world. For the survey question of "What are the greatest unmet needs regarding nAMD treatment?" 66% answered "reduced treatment burden" and 70% answered "long acting/sustained delivery" [54]. A total of 43% of

those surveyed admitted treating fewer than 10% of their nAMD patients at 4-week intervals for an extended period of time, and >50% would consider a product maintaining the most patients with quarterly (q12w) dosing. The 2018 survey answers are in line with those reported in the previous years.

Altogether, these findings demonstrate that the key goal for efficient management of nAMD is to develop new strategies and treatments that allow fewer injections but can reliably keep the retina dry, and less frequent monitoring without compromising efficacy. Emerging anti-VEGF treatments for nAMD include long-acting agents, sustained-release agents, combination strategies involving combined suppression of VEGF-A and new pathways, oral and topical agents [55–57].

Recommendations for Addressing the Gap

The decrease in vision in the long term observed in clinical studies could be due to the allowance of fluid recurrence with the PRN dosing and subsequent underdosing. The vicious circle of perceived/expected lack of efficacy/poor compliance/decline in VA over time should be broken. Several causes of long-term visual loss such as geographic atrophy [58, 59], and fibrosis [60, 61], should not be used as an excuse to mask the real major threat that is undertreatment. Patient education on risk/benefit would help, and this depends mostly on the treating physicians and their teams. VA can be preserved over the long term, for more than 5 years in many cases, if patients are treated more intensively/proactively and maintained on treatment.

The high treatment burden on patients, their caregivers, physicians, and the healthcare system should be lessened. This can be achieved by improved treatment strategies and new treatments that enhance VA and anatomic gains with fewer injections and less frequent clinic visits. Emerging anti-VEGF treatments for nAMD are expected to meet this need.

Conclusion

Anti-VEGF therapy has revolutionized visual outcomes in nAMD. However, the gains in real-world practice are not optimally sustained in the long term, as patients are often insufficiently treated. Reasons include the treatment burden for patients from numerous injections and monitoring visits, the cost to healthcare systems, and

the considerable impact on workflows in clinical practice. Poor patient education by the ophthalmologists, and especially a general mindset in the ophthalmological community that the long-term benefit with treatment is not possible, also largely contributes to undertreatment, poor patient compliance, and, ultimately, the loss of vision gains over time.

Lessening the treatment burden in nAMD for patients and healthcare providers remains a major challenge and an important unmet need, which may be addressed by promising new therapies that reduce the treatment burden while maintaining efficacy. In the meantime, an autocritical revisit of one's patterns of treatment are needed, and a change of mindset in the community regarding sustained long-term treatment and fighting the “myth” that prevention of vision loss in the long term is not possible under current therapy should be our priority.

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Author Contributions

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