Chapter

Management Strategies and Visual Results for the Treatment of Neovascular Age-Related Macular Degeneration

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Abstract

The purpose of this chapter is to examine the various treatment strategies used to manage neovascular age-related macular degeneration (nAMD). The chapter will focus on the three main strategies including fixed interval dosing, as needed Pro-Re-Nata (PRN) treatment and Treat-and-Extend (TAE), with its variant the Treat-Extend-Stop (TES) protocol. We will discuss the visual results of randomized clinical trials and retrospective studies using these methodologies and compare their outcomes, the pros and cons of each treatment strategy, as well as the underlying mechanisms that may explain these differences. The results of long-term extension trials following landmark randomized clinical studies and other long-term retrospective studies will also be compared to studies using a fixed interval dosing or the TAE/TES method. We will also focus on the visual results of the TES protocol and examine recurrence rates, proposing a definition of the recurrence of choroidal neovascularization (CNV) versus increased disease activity. These topics discussed will help optimize anti-VEGF treatment regimens for patients with nAMD over the long term.

Keywords: neovascular age-related macular degeneration (nAMD), anti-vascular endothelial growth factor (anti-VEGF), treat-extend-stop (TES), long-term management, recurrence

1. Introduction

Age-related macular degeneration (AMD) continues to be the leading cause of non-preventable blindness in the world and is the most frequent cause of blindness in industrialized nations [1, 2]. With an ever-aging population and age itself as the chief risk factor for the development of AMD, the burden of disease is expected to rise [3, 4]. Advanced AMD is defined by the presence of geographic atrophy or new onset of aberrant vessel growth from the underlying choroid, termed choroidal neovascularization (CNV) [5]. The development of CNV may lead to secondary subretinal or sub-retinal pigmented epithelial (RPE) hemorrhage or serous exudation, followed by fibrosis and scarring [5]. The degenerative form of the disease, "dry macular degeneration", may convert to the neovascularization form, "wet macular degeneration", at a rate of about 10–15% [6]. The natural disease course of nAMD over the long term is poor. Jager et al. demonstrated that at 2 years, patients lost on average 4 Early Treatment Diabetic

Retinopathy Study (ETDRS) lines [6]. They also found at baseline 20% of patients had 20/200 vision or worse, but at the end of 3 years, that percentage had increased to 76% of patients with vision 20/200 or worse [6].

Mitigating aberrant vessel growth and its sequelae have been a focus for treating neovascular AMD (nAMD). The use of argon and krypton photocoagulation on CNV was first evaluated by the Macular Photocoagulation Study Group (MPS studies) [7, 8], followed by photodynamic therapy (PDT) studied by the Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) and Verteporfin in Photodynamic Therapy (VIP) study groups [9, 10].

The isolation and discovery of vascular endothelial growth factor (VEGF) as the main driver of nAMD led to its targeting and inhibition as treatment [11]. This began with intravitreal injections of pegaptanib sodium (Macugen, OSI Pharmaceuticals, Melville, NY), a pegylated $VEGF_{165}$ specific aptamer, which demonstrated promising results in clinical studies and received fast-track approval from the FDA in 2004 [12]. Shortly thereafter, use of other anti-VEGF agents emerged with the positive results of off-label bevacizumab (Avastin, Genentech, San Francisco, CA) described in September 2005 [11, 13], which became a cornerstone of therapy for nAMD, along with its truncated Fab counterpart ranibizumab (Lucentis, Genentech, San Francisco, CA), later available in 2006 [14, 15]. Subsequently, the soluble VEGF decoy receptor, aflibercept (Eylea, Regeneron, Tarrytown, NY) has seen increased usage since its approval in 2011, due to its comparable efficacy to the other agents as well as some perceived advantages in clinical management with the possibility for less frequent dosing [16]. It has also demonstrated variable efficacy in clearing persistent fluid in eyes previously treated with bevacizumab or ranibizumab [17, 18]. Indeed, the use of anti-VEGF agents proved far superior to previous therapies, including laser photocoagulation and photodynamic therapy [7, 10, 15]. These extremely positive results caused a rapid paradigm shift in the management of nAMD and anti-VEGF agents quickly became the standard of care.

Although the anti-VEGF agent class is clearly superior, there are instances when PDT or thermal laser used in combination with anti-VEGF agents is appropriate. A commonly reported draw-back of thermal laser in the management of CNV is the high incidence of disease recurrence [19–21]. However, Adrean et al. have demonstrated in a case series of five eyes with peripapillary CNV, with subfoveal extension of exudate and fluid, that anti-VEGF therapy pretreatment may better help define the CNV area receiving laser treatment by first limiting the size of the CNV then causing resolution of the hemorrhage and exudate [22]. Following laser treatment, a subsequent anti-VEGF injection is given 1 week later to inhibit pathological CNV growth in response to the thermal laser [22]. This robust treatment method demonstrated that all study eyes were free of recurrence at a mean follow-up time of 24 months with average vision improving from 20/50 to 20/30 ($p = 0.0232$) [22].

Newer studies are underway examining other therapeutic options for the management of nAMD [23, 24].

2. Anti-VEGF treatment protocols and visual results

Three main treatment strategies have been developed to manage nAMD. The first method is fixed interval dosing, a mainstay of randomized clinical trials (RCT), where patients receive treatments on a monthly, bimonthly or quarterly interval based on the anti-VEGF agent. Shortly thereafter, the Pro-Re-Nata (PRN) method was introduced, where patients were treated as needed based on optical coherent tomography (OCT) status, usually preceded by three monthly

anti-VEGF loading doses. Another method developed was the Treat-and-Extend regimen (TAE). Patients are typically treated until a dry macula is obtained, and then the time interval between injections is gradually increased, usually by one to two-week intervals. These distinct treatment methods produce comparable visual and anatomic outcomes in the short term (≤1–2 years). However, in the long term (≥3 years), small differences in these outcomes are substantially amplified.

2.1 Fixed interval dosing

The treatment of nAMD using anti-VEGF therapy began with fixed interval dosing, which is the mainstay of the initial, landmark RCTs. Subjects with CNV typically have scheduled examinations with SD-OCT and receive intravitreal injections every 4 to 6 weeks. Patients may also get fundus photos (FF) and fluorescein angiography (FA) initially and at other predetermined time intervals [14].

This treatment strategy is the initial treatment regimen that demonstrated superior efficacy compared with previous methods such as thermal laser and verteporfin, as well as a largely positive safety profile, in RCTs and clinical practice. In the seminal anti-VEGF RCTs, namely the Ranibizumab for Neovascular Age-Related Macular Degeneration (MARINA), Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration (ANCHOR), and Twelve and Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration (HARBOR) trials, treatment arms with monthly ranibizumab injection demonstrated an average visual improvement of +6.5 to +11.3 ETDRS letters [14, 15, 25, 26]. Subsequent trials such as the ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration (CATT) and alternative treatments to inhibit VEGF in age-related choroidal neovascularization (IVAN) trials reported, at minimum, similar clinical efficacy of ranibizumab and bevacizumab in each of the treatment arms (Δ = 1.4 letters CATT 24 months; Δ = 1.3 letters IVAN 24 months) [27–30]. Intravitreal aflibercept reported a composite 8.4 ETDRS letter gain at 52 weeks in the VIEW 1 and VIEW 2 RCTs and met non-inferiority criteria when compared with ranibizumab treatment arms [16]. Yet one study, the PIER study, evaluated fixed interval dosing with ranibizumab, at a greater time interval between injections and showed poorer overall outcomes compared to monthly treatments. Patients were randomized 1:1:1 to receive 0.3 mg ranibizumab, 0.5 mg ranibizumab, and sham injections, respectively, at quarterly intervals [31]. At the end of the first year, patients in each of the treatment groups had already experienced visual declines below baseline vision [31], and by the end of the second year, visual loss was even more dramatic (e.g. −0.2 at 1 year and −2.3 letters at 2 years for 0.5 mg ranibizumab vs. onset study vision) [32]. While better than sham injections, these results were strikingly worse compared to monthly fixed dosing in previous RCTs (+6.5 to +11.3 ETDRS letters vs. baseline). Study patients were subsequently rolled-over to monthly injections, and although some vision was able to be recovered (+2.9 to +4.3 ETDRS letters), visual acuity (VA) was never able to be restored to levels consistent with monthly dosing [32]. This was one of the first examples that reduced treatment in a RCT had decreased visual outcomes and that more frequent dosing of anti-VEGF agents resulted in better visual outcomes.

Then multiple retrospective studies describing the success of monthly dosed anti-VEGF injections were published, with certain retrospective studies demonstrating efficacy over the long term [33, 34]. For example, Peden et al. retrospectively reported average visual results of 14.0 letters, 12.2 letters and 12.1 letters at an average treatment duration of 5, 6 and 7 years, respectively, using a fixed monthly injection regimen averaging 10.5 injections per year [34]. However, due

to the treatment and potential economic burden, injection fatigue to both patient and physician, as well as the concern for systemic arteriothrombotic events (ATEs), other treatment strategies have been developed.

2.2 Pro-Re-Nata (PRN) dosing

The first response to fixed interval dosing was the development of a treat as needed (PRN) dosing regimen, which gained rapid acceptance after initial RCTs evaluating its efficacy at 1–2 years compared favorably to monthly fixed dosing. Patients receiving this strategy typically receive loading injections, most commonly once per month for 3 months, and then injections are given or held based on exam. If patients' vision and disease stabilize, then injections are held. If there is persistent fluid or exudate, anti-VEGF therapy is continued monthly until a "dry" macula occurs, typically determined on SD-OCT. Otherwise, changes such as decreased vision, new onset fluid or growth of lesion size, among others, as demonstrated by clinical exam, OCT, FA or other diagnostic methods typically drive renewal of treatment [27, 28].

The HARBOR and CATT trials reported clinically comparable visual gains between monthly fixed dosing and PRN study arms at year one [25, 27]. Although in the Harbor trial, examining ranibizumab, the PRN arm was unable to meet the pre-specified, non-inferiority outcomes even at 1 year compared to fixed-monthly injections [25]. On the other hand, even though the CATT study reported worse vision in the PRN group in both the bevacizumab or ranibizumab arms, it met the non-inferiority criteria compared to fixed monthly dosing [27]. Interestingly, these two landmark RCTs had different non-inferiority criteria, differing by only one letter [25, 27]. Regardless, by the end of year two, visual outcomes in the PRN treatments arms was significantly worse than the fixed monthly dosed groups in both studies ($p < 0.05$) [26, 28]. In fact, the HARBOR study concluded that at the end of 12 months, monthly dosing of ranibizumab proved superior over PRN dosing [26]; and, the CATT study likewise summarized that "[PRN] resulted in less gain in VA, whether instituted at enrollment or after 1 year of monthly treatment [28]." The IVAN study, later conducted in the United Kingdom, concluded that visual outcomes using the PRN method were "equivalent" to continuous treatment (−0.4 letters, 95% Cl, −2.40 to 1.70) in the first year of evaluation [29]. However, by the end of the second year, they reported that the "reduction in the frequency of retreatment resulted in a small loss of efficacy irrespective of drug," and demonstrated that discontinuous treatment resulted in 1.6 letters lost compared to monthly fixed dosing, although this was not statistically significant ($p = 0.18$) [30]. These, arguably small, differences were further amplified when this treatment methodology was continued over the long term. Two landmark extension studies of RCTs demonstrated this effect: The Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration (CATT-5) trial and the Seven-year Outcomes in Ranibizumab-treated Patients in ANCHOR, MARINA, and HORIZON: a Multicenter Cohort Study (SEVEN-UP). In these two studies, most patients were transitioned or maintained on a PRN schedule following the conclusion of their respective RCTs. By the end of year 5 of the CATT-5 study, patients on average lost 3 ETDRS letters from baseline and 11 letters from the 2-year endpoint of the original CATT study [35]. Moreover, 20% of eyes had vision 20/200 or worse compared to only 6% at study baseline, which improved to 5% in years 1 and 2 [35]. Overall, 36.4% of eyes lost ≥5 letters from baseline and 54.6% of eyes lost ≥5 letters from the end of year 2 [35]. In fact, nearly 24% of eyes lost ≥15 letters baseline and 29% lost ≥15 letters from the original study conclusion [35]. In the SEVEN-UP study, 37% of eyes had vision 20/200 or worse at the end of

7 years, with 34% of eyes losing ≥15 letters for an average decline of 8.6 letters from ANCHOR or MARINA baseline [36]. Strikingly, this was a change of −19.8 letters from the peak vision obtained at the end of the ANCHOR and MARINA trials [36]. In fact, most eyes lost vision at the end of the SEVEN-UP study when compared to any of the presenting or exiting vision of its preceding studies (56.9% vs. MARINA or ANCHOR entry; 84.6% vs. MARINA or ANCHOR exit) [36]. Similar trends have been observed in clinical practice and documented in multiple retrospective studies, demonstrating good clinical outcomes in the near term which deteriorated over time, commonly below baseline levels. In a study by Rasmussen et al., 192 eyes receiving PRN injections had an improvement of 3.4 letter above baseline at the end of 1 year, which regressed to 1.4 letters at the end of year 4 [37]. This was one of the few PRN studies that demonstrated an average final vision above baseline, although this was still not statistically significant [37]. Others, such as those by Gillies et al. [38], Zhu et al. [39], Haddad et al. [40], the PACORES study group [41] and Westborg et al. [42] recorded average visual losses from as little as −4.3 letters to as much as −25.4 letters from peak visual gains, when studied over the long term.

2.3 Treat-and-Extend (TAE) and Treat-Extend-Stop (TES) methods

Although initially well received, small deficiencies in visual and anatomic outcomes under the PRN strategy were amplified both in RCTs and clinical practice, particularly when patients required anti-VEGF injections over the long term. Thus, in response, a graduated treatment protocol, termed "Treat-and-Extend" (TAE), along with its variation, the "Treat-Extend-Stop" regimen developed by Adrean et al. [43], was created to improve patient outcomes while keeping the benefits of reduced treatment burden. Due to the success of this method, it is currently the most widely used treatment protocol of retinal specialists in the United States [44]. Patients treated with this strategy are typically treated with a minimum of 3 monthly loading doses until there is clinical resolution of fluid and SD-OCT demonstrates a "dry" macula [43]. Treatments are then lengthened by 1–2-weeks based on evaluation at each visit [43]. If a "dry" macula is maintained on SD-OCT, then the time interval is increased to a typical maximum of 10–12 weeks [43]. If at any time patients experience a decrease in vision or increase in exudation as quantified on SD-OCT, then treatment intervals are adjusted, usually decreasing by 1–2 weeks, to adequately control the disease process [43]. Some patients can reach maximum extension, and therefore continue receiving treatment every 10–12 weeks indefinitely; other patients never reach maximal extension, but instead require constant adjustment or continuous treatment at shorter intervals [43]. If patients are determined to be failing one anti-VEGF agent after 3–6 intravitreal injections, the anti-VEGF agent is typically changed.

The TES strategy was developed for patients achieving a maximal extension to further decrease treatment burden [43]. Using the TES method, patients who reached a maximum extension of 12 weeks then receive 2 additional injections, each 12 weeks apart, with an FA performed at the second 12-week visit to evaluate the CNV [43]. Patients are then examined 12 weeks later [43]. If the macula was "dry" at that point, as determined by SD-OCT, patients are then considered to be in disease remission and further injections are held [43]. Next, patients are carefully monitored for any signs of disease recurrence with a monitoring phase beginning 4 weeks later [43]. Evaluation intervals are then progressively lengthened at 2-week intervals until 12 weeks are reached, at which time patients are then monitored indefinitely at quarterly intervals [43]. If at any time, patients notice decreased vision or an increase in metamorphopsia, they are instructed to return immediately to the clinic for re-initiation of treatment, and the TES protocol is restarted from the beginning [43].

In RCTs and clinical practice, the TAE method has demonstrated visual outcomes similar to monthly fixed dosing at a decreased increased injection frequency, and superior to those reported using the PRN method. In the Comparison of Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration Accord to LUCAS Treat-and Extend Protocol (LUCAS) trial by Berg et al., bevacizumab and ranibizumab were found to be equivalent with an average of 7.9 and 8.2 letters gained, respectively, at the end of the first year [45]. In the second year, bevacizumab and ranibizumab continued to demonstrate efficacy with average visual improvements of 7.4 and 6.6 letters from baseline, respectively [45]. Interestingly, a greater number of injections were given in the bevacizumab group than in the ranibizumab group [45]. Around the same time, Wykoff et al. published a Prospective Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration [46]. Wykoff et al. demonstrated at the end of 1 year that TAE dosing of 0.5 mg ranibizumab resulted in similar outcomes compared to fixed monthly dosing, with average visual gains of 10.5 and 9.2 letters respectively [46]. The comparative efficacy between TAE and fixed monthly administration has also been described in numerous other studies, both retrospectively and prospectively. For example, Chen et al. demonstrated in a retrospective analysis that eyes undergoing monthly vs. TAE treatment at 1 year on average had a visual difference of −0.5 letters ($p = 0.81$) [47]. Additionally, Abedi et al. demonstrated in a prospective cohort study of 120 eyes, average visual gains of 9.5 letters and 8.0 letters at 12 and 24 months, respectively, which were comparable to those of the pivotal clinical trials [48]. These visual outcomes may also be maintained over the long term. For example, in a retrospective cohort study by Mrejen et al., 210 study eyes, with a retention rate of 62.9%, at an average of 3.5 years, had visual improvement of 20/90 from study baseline to 20/75, or approximately one line of improvement ($p < 0.05$) with an average of 8.3 injections per year [49]. Perhaps the longest studies evaluating this method are those performed by Adrean et al., specifically using the TES variation. In one study, patients received TES treatment for an average of nearly 3 years until the disease was controlled to remission, and patients were transitioned to quarterly follow up, as described previously, without injections [43]. At this point, the average visual improvement was approximately +7.5 ETDRS letters, improving from 20/70 to 20/50, with 60% of eyes achieving 20/40 vision or better [43]. At study conclusion, accounting for CNV disease recurrence and re-initiation of treatment, a total of 38.1% of eyes gained 3 or more lines of vision, whereas only 2 eyes of a single patient (4.8%) lost 3 lines of vision due to development of geographic atrophy [43]. In another study, Adrean et al. demonstrated that long-term treatment of 71 study eyes with nAMD, using the TES protocol, resulted in average visual gains of 9.7 letters over an average treatment period of 6.5 years [50]. Notably, this visual improvement was maintained over an average follow-up period of 8 years, with only a slight decrease to a final average visual improvement of 8.7 letters [50]. The percentage of eyes gaining 3 or more lines of vision at final follow-up in this study at 8 years, was 35.2%; conversely, 9.9% of eyes lost 3 or more lines [50]. In fact, these visual outcomes are similar to the proportion of eyes gaining at least 3 lines of vision found in monthly fixed dosing RCTs, such as MARINA (33.3% with 0.5 mg ranibizumab) [14], ANCHOR (41% with 0.5 mg ranibizumab) [15], and HARBOR (34.5% with 0.5 mg ranibizumab) [26] at the final study endpoint of only 2 years.

Both RCTs and retrospective studies using the TAE/TES method have demonstrated superior visual outcomes compared to PRN studies. In a systematic review by Rufai et al., which included the assessment of 748 eyes undergoing the TAE protocol, the one-year BCVA improvement was 8.9 letters, compared to the 3.5 letters reported by Chin-Yee et al. in a separate systematic review regarding the PRN method [51]. Head to head studies, such as those by Chin-Yee et al., demonstrated an average 10.4

letter improvement in the TAE group vs. 5.4 letters in the PRN group at 12 months, with the TAE group receiving about 3.5 more injections on average [52]. Likewise, in a study by Oubraham et al., average visual acuity was greater in TAE treated eyes compared to PRN treated eyes by 8.5 letters with an average of 2.7 more injections [53]. Interestingly, the number of follow-up visits was similar (8.5 vs. 8.8, TAE vs. PRN, p = 0.2085) [53]. The most interesting studies might be those conducted by Hatz et al. and Cohen et al. As with the rescue effect observed in the patients rolled-over from PRN to monthly dosing in the PIER trials, patients transitioning from the PRN to the TAE method demonstrated improved vision despite having a greater number of office visits in the PRN group [54, 55]. Although there is no long-term head-to-head comparison study between TAE/TES vs. PRN treatment methods in RCTs or private practice, a comparison of these outcomes individually reveals that the TAE/TES method is superior. RCTs, such as the CATT-5 and SEVEN-UP studies, along with many retrospective studies employing the PRN method beyond an average follow-up time of 3 years (up to 7 years) have demonstrated average visual changes of +1.4 to −19.3 letters from baseline vision [35–42]. Conversely, prospective and retrospective data have reported visual increases of 5–9.7 letters for similar time intervals in eyes managed by a TAE/TES strategy [43, 49, 50].

3. Potential mechanisms of management strategies for disease and visual outcomes

Various factors have been implicated in the variation of visual outcomes for eyes with nAMD managed by anti-VEGF therapy [6]. For example, older age or male gender has been associated with increased exudative disease and the need for retreatment [56]. However, recent studies have suggested that some factors, such as initial presenting vision, are predictive of the long-term visual gains [57]. Additionally, other groups have examined CNV lesion type and demonstrated that there was a differential response to anti-VEGF therapy and visual outcomes [14, 15, 49]. Therefore, it appears that the optimization of these factors may lead to more favorable responses in patients' visual outcomes, especially over the long term.

Shah and Del Priore in a large meta-analysis described that patients' presenting vision contributed to as much as 90% of the final visual outcomes obtained using anti-VEGF therapy [57]. Poorer presenting vision was typically due to longer delays before the initial presentation to the physician, with patients reporting a longer duration of symptoms before seeking care [57]. The greater the delay was prior to initiating anti-VEGF therapy, the worse the final achievable vision [57]. Interestingly, they also noted that patients with worse initial vision also had greater amounts of active exudation and more commonly presented with type-2 classic CNV [57]. It is generally accepted that in the typical course of the disease, if left untreated, type-1 occult lesions often progress to mixed and, subsequently, classic CNV [58]. Over time, uncontrolled disease activity and exudation perpetually cause damage to the neurosensory retina and RPE, ultimately leading to subretinal fibrosis and irreversible vision loss.

Distinct lesions respond differently to anti-VEGF therapy. Early RCTs, for example, when comparing the results achieved from monthly dosing of 0.5 mg ranibizumab in the MARINA study for minimally classic or occult lesions to the predominantly classic lesions evaluated in the ANCHOR trials, demonstrated that visual gains were greater in the classical CNV study [14, 15]. While this seems to contradict the findings of Shah and Del Priore [57], this is because patients with subretinal fibrosis or signs of advanced macular degeneration were excluded. Additionally, patients' baseline vision in the ANCHOR trial had to be better than

20/320 to be included in the trial, which limited many patients with advanced exudative disease [15]. While visual gains were better realized in the ANCHOR study, possibly due to poorer presenting vision, a ceiling effect was likely encountered in the MARINA study. For example, the average presenting vision of the 0.5 mg ranibizumab arm of the ANCHOR study was 47.1 ± 13.2 letters [15], whereas it was 53.7 ± 12.8 letters in MARINA [14], a difference of nearly 7 letters. At the end of year one, the study eyes in the ANCHOR study had gained an average of 11.3 letters in the 0.5 mg ranibizumab group [15] compared to 7.2 letters in the MARINA study [14], for average final VA of 58.4 vs. 60.9 letters respectively [14, 15]. Other reasons, such as the location of the CNV or exudation in relation to the fovea may also play a factor. Classic lesions outside of the fovea with subfoveal leakage and exudate may have better visual outcomes since the CNV itself is not subfoveal. As the fluid and exudate dissipate with therapy, the subfoveal architecture remains largely intact with preservation of the central photoreceptors and retinal pigment epithelium, allowing for increased visual gains.

As described previously, there are relatively few studies examining the long-term treatment results of anti-VEGF therapy. Those describing the PRN strategy have been the most numerous, while those examining the TAE/TES or monthly dosing regimens are substantially fewer. There are even fewer studies that characterize lesion type or subtype and their response to anti-VEGF therapy over 2–3 years. One study, by Mrejen et al., examined the response of anti-VEGF treatment administered using a TAE strategy in eyes with different CNV lesion subtypes [49]. Occult lesions were found to have the best initial presenting vision, which was maintained throughout 4 years, although these patients also received an average of 0.6–2.2 more injections compared to other groups ($p < 0.05$) [49]. Preservation of vision tends to be greater in occult or mixed lesions as opposed to classic lesions [49]. These results were replicated in a similar study by Berg et al., which demonstrated that longer-term anti-VEGF therapy using a TAE method resulted in better visual maintenance in eyes with occult or mixed lesions over classic lesions or retinal angiomatous proliferation (RAP) [59]. Together with the evidence described above, reporting that eyes with delayed initial presentation and worse baseline vision having greater evidence of active exudation as well as the progression from type-1 occult to type-2 classic lesions, it is apparent that early diagnosis and thorough control of nAMD should result in the best possible visual outcomes. Otherwise, a CNV left untreated or inadequately treated may lead to progressive retinal damage, which generally manifests as increased fluid or exudation, which then leads to end-stage disease such as atrophic and fibrovascular scarring, ultimately resulting in decreased vision.

As we have previously noted, slightly worse vision due to PRN treatment in short-term studies has resulted in substantially worse vision over the long term when compared to monthly fixed or TAE/TES dosing strategies, even when baseline characteristics are otherwise comparable. This may be, in fact, due to the reactive nature of the PRN strategy, leading to considerable delays in recognition of increased disease leading to suboptimal treatment. Due to the inherent difficulty in scheduling office visits and the unreliability of patients to report increased disease (caused by several factors, such as the subtlety of symptoms confounded by the vision in the fellow eye), by the time the patient presents for follow-up, even if scheduled ahead of time, new onset or progression of active disease may have already occurred. It may be, in fact, that the fewer injection numbers reported by PRN studies, particularly in the long term, are not a result of better disease control, but are instead demonstrative of missed opportunities for adequate disease control.

Indeed, the number of injections is a key factor associated with final visual outcomes [60]. This may be due to greater numbers of injections maintaining a therapeutic level of VEGF inhibition in the eye. In a study by Lumbroso et al., vessel

proliferative cycling of CNV in the presence of anti-VEGF activity was examined [61]. The proliferation of aberrant vessels in CNV appears to cycle through a series of predictable stages after anti-VEGF inhibition [61]. Pruning begins within 24 h of initial anti-VEGF injection and progresses to maximal inhibition at 6–12 days [61]. As anti-VEGF levels fall, the sprouting of new vessels and angiogenic leakage may then develop anywhere from 20 to 50 days later [61]. Interestingly, with increasing numbers of anti-VEGF injections, likely maintaining steady inhibitory concentrations within the eye, the time between each proliferative cycle lengthens [61]. Neovascular vessel burden decreases and, instead, the central vessels from which they sprout and open increase in size [61]. This process may also explain why untreated occult disease may eventually progress to type-2 lesions, followed by fibrovascular scarring and irreversible vision damage. Due to the reactive nature of the PRN strategy described above, poor inhibition on this mechanism of neovascular proliferation likely occurs. For example, after transitioning all original treatment groups in the CATT, MARINA and ANCHOR trials to the PRN method for long-term treatment, the number of eyes with residual fluid at the end of the CATT-5 and SEVEN-UP trials was 68 and 83%, respectively [35, 36]. Moreover, 24.5% of CATT-5 study eyes were found to have leakage on FA [35]. Likewise, 48% of eyes had active or probable leakage of FA in the SEVEN-UP study [36]. Interestingly, despite 68% of eyes having intraretinal or subretinal fluid, and nearly half of eyes with leakage on FA, only 46% of eyes were receiving ongoing treatment at the end of the SEVEN-UP study [36]. Although it is unclear which of the factors described above may have contributed to the visual decline of the study patients in these two RCTs, the mismatch between eyes with active disease or persistent fluid/exudation and those that were receiving active treatment suggests that adequate disease follow-up and control may not have been well established. Moreover, this is complicated by the fact that, as reported in both SEVEN-UP and CATT-5 studies, the subretinal fluid itself was not significantly associated with decreased vision, while intra-retinal fluid was [35, 36]. However, the SEVEN-UP study group suggested that subretinal fluid may be relevant in the context of generally uncontrolled neovascular disease progression [62]. Along with hemorrhage and exudation, permanent damage to the neurosensory retina and surrounding structures may also lead to macular atrophy, one of the strongest drivers of decreased vision in the long-term treatment of nAMD [62]. The CATT study group, on the other hand, proposed that subretinal fluid may, in fact, be protective against the development of geographic atrophy [63]. However, these two studies differ in their respective definitions of atrophic disease. The CATT study group suggested that the atrophic macular lesions they describe may be clinically indistinguishable from those arising from non-neovascular origins, mainly geographic atrophy [63]. Macular atrophy may be a separate entity since it lacks the classic anatomical features of geographic atrophy [62]. Thus far, it appears that timeliness and greater numbers of injections generally lead to better anatomical and visual outcomes. Future studies further elucidating these factors may help better optimize treatment strategies.

When comparing the number of injections patients received, the average number of injections received was greatest in the monthly dosed regimens, followed by the TAE/TES method, and finally PRN. For example, Peden et al. reported an average of 10.5 injections per year at 7 years, using the monthly fixed interval dosing [34]. Adrean et al. in their consistent long-term anti-VEGF study, utilizing the TES strategy, were performing 9.6 injections per year at 6.5 years and 8.1 injections per year at the final follow-up at 8 years [50]. Conversely, RCTs utilizing the PRN method reported an average of 5.1 injections per year in the CATT-5 study [35] and 2 injections per year in the SEVEN-UP study after exit from the HORIZON follow-up trial [36]. Interestingly, in a subgroup of patients that received more

injections (3.2 per year) in the SEVEN-UP trial, their vision was significantly better than other study participants [36]. As described earlier, the number of injections has been demonstrated to be an independent factor positively contributing to visual improvement. Again, this phenomenon may be explained in the context of increased injections leading to maintenance of adequate inhibition of VEGF, which in turn, inhibits vessel growth and increases the time for neovascular vessel proliferation cycles. While some studies demonstrate that the PRN method has fewer injections than TAE/TES dosing at a 1-year endpoint, they have similar number of visits, with poorer visual outcomes [64].

Taken together, these lines of evidence suggest that the improper timing of the PRN method to detect and treat disease, as well as the subtherapeutic dosing of anti-VEGF agents due to less frequent injections, leads to a greater exudation, hemorrhage, and progressive macular damage, ultimately resulting in poorer vision. Monthly dosing, on the other hand, is superior for controlling disease. However, this method may not scale as the population ages and the incidence of nAMD rises. Fixed monthly dosing may lead to overtreatment, injection fatigue, as well as increased costs and the potential for increased risk of adverse events. The TAE/TES method, with progressively lengthening treatment and observation times, individualized to each patient, may maintain adequate intravitreal anti-VEGF levels which allows for the lengthening of neovascular vessel proliferation cycles. The long-term visual outcomes of the TAE/TES method compare favorably to the fixed dosing method, with fewer office visits and injections. Future therapeutic advancements may further optimize nAMD management.

4. Dosing strategy and effect on disease activity, recurrence and visual outcomes

Various studies have attempted to define characteristics of disease control and make better assessments for when to continue treatments consistently or possibly discontinue treatment. The most commonly used characteristics are changes in visual acuity and the presence or absence of retinal fluid, typically based on SD-OCT data regardless of the dosing strategy utilized [65, 66].

A consensus article by Amoaku et al. attempts to characterize the degree of response eyes have to anti-VEGF therapy [66]. Eyes are categorized as good, partial, poor or non-responders. Good responders are free of fluid or have a central retinal thickness (CRT) reduced by >75% following the initial loading phase of therapy, typically the first 3 monthly injections. Visually, these eyes demonstrate an improvement of >5 ETDRS letters or achieve greater than 70 total ETDRS letters, if a ceiling effect is present. Partial responders have less CRT reduction (25–75%) and may have some persistent subretinal or intraretinal fluid. Visual improvement is generally limited to 1–4 letters gained. Poor responders have even less CRT reduction (0–25%) as well as persistent fluid on SD-OCT. Visual acuity is typically unchanged from baseline to a loss of −4 letters. Finally, non-responders have unchanging or increasing CRT, fluid or pigmented epithelial detachment (PED), with eyes losing 5 or more letters. Management of nAMD can be stratified based on these characteristics. For example, good and partial responders may continue their current anti-VEGF regimen if their vision or morphology is maintained. If there is decreased vision or indicators of poorer morphology, the time interval between treatment should be reduced, and if treatment has been maintained at 4-week intervals without an improvement in morphology, a switch in anti-VEGF agents is needed. Other studies have characterized response based on lesion type, concluding that occult and mixed lesions generally respond better to anti-VEGF

therapy than classic or RAP lesions [49, 59]. Moreover, not all retinal fluid is equal, as some groups have suggested that subretinal fluid is protective against geographic atrophy [63]. Nonetheless, many agree that achieving a dry macula is necessary to prevent retinal damage over the long term and is essential for the improvement and preservation of vision.

When considering the dosing regimen, Amoaku et al. suggested that more frequent dosing tends towards improved visual outcomes, likely due to proactive disease control that is not realized in PRN methods which often result in under-treatment [66]. Other factors such as antibody neutralization and tachyphylaxis may also affect the success of anti-VEGF treatment regardless of factors such as presenting vision or morphology [66]. Therefore, it appears that a patient's response to anti-VEGF therapy is a complex interplay between multiple factors that are attributable intrinsically to the patient as well as their treatment history.

One key factor in a patient's treatment history affecting visual outcomes is the degree of disease control. However, there is loose language surrounding the topic of active disease progression or disease recurrence. Many studies have described recurrence as any new onset of fluid or exudation regardless of time, thus implicitly suggesting that active disease is controlled as soon as the macula is deemed "dry". Other studies use the term "disease recurrence" to mean new onset CNV or exudation after disease remission, for example, a minimum time criterion of 4 months with no evidence of fluid or exudation ("active disease") [40, 43]. At present, there is no formal definition accepted. This is problematic because, as discussed earlier, neovascular vessel proliferative cycling times may be lengthened with successive anti-VEGF injections, leading to clearing of fluid, but the underlying disease may not be entirely controlled. Thus, those that conclude active disease is controlled after the fluid has been eliminated from the macula after a single injection may be mistaken, and the clearing of fluid observed may be short-lived. Indeed, this fact is most concerning for patients undergoing anti-VEGF treatment with a PRN regimen, as follow-up visits which demonstrate "absence" of disease and subtle visual changes may ultimately cause delays in treatment and progressive retinal damage. This phenomenon is less likely to be present in TAE/TES or monthly fixed dosing strategies since injections are more frequent and scheduled. However, a lack of consensus definition confuses the reported outcomes in literature and serves to make comparisons between studies more challenging. Given that previous in vitro studies have demonstrated that new pathologic vessels may develop after a single anti-VEGF injection of up to 62 days later [61], true disease remission logically should be at minimum outside of this time. Thus, disease remission may be defined as no fluid recurrence within 4 months and that at this point the disease is considered quiescent. If fluid occurs outside of the 4-month period, it is likely that a true recurrence of nAMD has occurred. However, any increase of subretinal or intraretinal fluid that occurs during active treatment in the TAE/TES protocol should be defined as an increase in disease activity and the time interval should be decreased accordingly, depending on the amount of increased disease activity. If patients are in the loading or maintenance phase of a TAE/TES protocol and are in the 5–8 week treatment range, then the time interval between injections should be reduced by 1–2 weeks. If patients are being treated at the 10–12 week range and there is a small amount of increased exudation, then the time interval again may be reduced by 2 weeks. However, if there is a significant increase in disease activity, then the time interval should be reduced more aggressively, potentially even restarting the TAE/TES protocol. If patients continue to have increased exudation and the time interval between anti-VEGF injections has been decreased to the 4–6 week range, then likely the anti-VEGF agents needs to be switched [43, 45, 50]. If patients are being

treated with a PRN methodology, and there is increased fluid at a time interval of less than 4 months without treatment, again this should be considered increased disease activity. If increased exudation occurs outside of 4 months, this should be considered a true recurrence.

Reports on true CNV disease recurrence are currently limited. Two retrospective studies have reported this phenomenon. In the first, Haddad et al. utilized a PRN dosing method in 132 eyes over an average follow-up of 7.75 years [40]. Eighty-three (63%) eyes experienced long-term remission without requiring treatment for 1 year at least one time during the duration of the study [40]. However, among them, 42 (51%) eyes experienced a true recurrence of CNV [40]. The average vision of the entire cohort improved 5.0 letters after 1 year compared to baseline [40]. However, by the end of 7.75 years, this visual improvement was not maintained and decreased to −3.4 letters below baseline, a total loss of 8.4 letters [40]. Conversely, in a study by Adrean et al., 143 of 385 eyes (37.3%), treated with a TES protocol, experienced long-term disease remission with a minimum treatment cessation period of 4 months [43]. Prior to this time, these eyes were treated with a TES protocol for an average of 33 months [43]. The average initial presenting vision was 20/70 and improved to 20/50 at the completion of the treatment phase, or approximately 7.5 ETDRS letters [43]. The average time to true disease recurrence was 14 months later and occurred in 42/143 (29.4%) eyes [43]. At this point, average vision decreased to 20/60, with 54.8% of eyes experiencing a recurrence without a decrease in vision [43]. However, once eyes were restarted on the TES protocol, average vision recovered to 20/50 and was maintained throughout the remaining average 27 months of follow-up [43]. Although the criteria for remission of disease are different between these two studies, the average time observed of quiescent disease not requiring treatment was around 1 year [40, 43]. Notably different, however, is that the final vision of eyes treated with the more robust TES method was better and was able to be salvaged should a recurrence occur [40, 43]. This is likely due to the undertreatment of active disease that is commonly experienced from PRN methods, even if eyes demonstrate signs of good response [66]. Eyes demonstrating good response under a PRN method may require more vigilant monitoring over a greater period of time before one may conclude that active disease has been controlled. On the other hand, eyes that have received more robust treatment under the TES method may be carefully monitored at longer intervals if good response has been demonstrated throughout the course of treatment for active disease.

5. Conclusion

In this chapter, the three main treatment strategies to treat nAMD were presented and discussed. The first strategy examined was the fixed dose treatment method, where anti-VEGF agents are given on a routine basis, typically monthly or bimonthly after an initial loading phase. The advantage of this method is that it has been proven successful in multiple landmark clinical trials and patients may expect potentially the best visual outcomes. Fixed dosing disadvantages include the lack of individualized treatment with potentially no endpoint and the possibility of being overtreated. There is a potential for more episodes of endophthalmitis with more injections given and the chance for systemic effects, although this is still debated. The next treatment strategy presented was the PRN methodology, where patients are typically given a loading dose of three monthly anti-VEGF injections and then monitoring is begun once the macula is dry. Patients are then

treated only after the detection of new-onset decreased vision or increased fluid. The advantage of this treatment methodology is that patients receive fewer injections with potentially fewer systemic and ocular side effects. However, there is the potential for delayed detection of decreased visual or anatomic damage, increasing the risk for undertreatment with this methodology. Visual results of this method have definitely proven inferior compared to other dosing regimens, particularly over the long term. The final treatment strategy presented was the treat-and-extend regimen with its variant treat-extend-stop. After three loading doses of anti-VEGF therapy for nAMD, patients are then extended by 2-week intervals once a dry macular is achieved. In some patients, the therapy is stopped after patients are given two injections 12 weeks apart and held at the third 12-week interval, after which careful monitoring of patients' visual function and macular changes is begun. This personalized anti-VEGF regimen offers the greatest potential for success. The TAE/TES regimen may be the best choice for managing patients with nAMD, particularly over the long term, regardless of the choice of the anti-VEGF agent. The TAE/TES method provides comparable visual results to monthly fixed interval dosing, however at a decreased treatment burden and has the potential for decreased adverse events. This proactive and patient-specific method also has many benefits over the PRN strategy, including but not limited to greater visual improvement, better maintenance of visual improvement over the long term, increased potential for disease remission, fewer rates of CNV recurrence, and the ability for recovery of vision after recurrence.

This chapter also discussed the definition of recurrence versus increased disease activity. Increased disease activity was defined as increased intraretinal or subretinal fluid with potentially decreased vision and increased metamorphopsia that occurred during active treatment. If patients fail to respond to any one agent after 4–6 monthly anti-VEGF injections and still have worsening subretinal or intraretinal fluid, these patients may meet the definition of primary treatment failure and the anti-VEGF agent can be switched. If patients are in the extension part of the TAE/TES protocol and there is increased fluid and exudation, the time interval between treatments should be reduced by 1–2 weeks if there is minimally increased exudation. If there is a significant increase in exudation or hemorrhage, then the time interval should be decreased more aggressively, potentially restarting the TAE/TES protocol. Patients with nAMD likely require at least 1 year of therapy, extended to 12-week treatment intervals, before treatment cessation is considered since there is a subset of patients of whom are delayed responders and may demonstrate increased vision over a longer time frame. A true disease recurrence would be defined as one where a CNV shows increased exudation and hemorrhage after 4 months of no treatment and careful monitoring. This true recurrence rate was found to be 29% in the TES protocol and patients with a true recurrence had overall visual outcomes comparable to their vision at treatment cessation after re-initiation of anti-VEGF treatment. It is likely that partial, poor or non-responders are more inclined to receive consistent treatment at time intervals in the 4–8 week range, and these patients' visual acuity over the long run may be best maintained with this dosing interval. This conservative calibration strategy thus strives to proactively optimize the treatment regimen to the patients' response.

Additional studies, particularly prospective randomized clinical trials evaluating the response of various treatment methodologies over the long term as well as those exploring the mechanisms underlying clinical outcomes, will help further optimize anti-VEGF therapy and spur the development of novel methods for the treatment of nAMD.

Conflict of interest

None.

Notes/thanks/other declarations

None.

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