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Evolution of treatment paradigms in neovascular age-related macular degeneration: a review of real-world evidence

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ABSTRACT

The aim of this work was to evaluate the contribution of real-world evidence (RWE) in changing anti-vascular endothelial growth factor (VEGF) therapy treatment practices and improving real-world treatment strategies for neovascular age-related macular degeneration (nAMD).

A PubMed literature search was performed to review the large number of English-language studies conducted to investigate the real-world effectiveness of anti-VEGF (aflibercept and ranibizumab) treatment paradigms available for nAMD.

The evidence for pro re nata (PRN), treat-and-extend (T&E) and fixed bimonthly dosing regimens for anti-VEGF treatment of nAMD were reviewed and findings are summarised. RWE demonstrated that T&E regimens optimise visual outcomes while reducing burden on patients, clinics and physicians, compared with both fixed-dose and PRN regimens.

RWE has helped to develop and improve real-world treatment strategies in nAMD, with the aim of optimising visual outcomes and reducing treatment burden in clinical practice. Of the various regimens, a T&E regimen is most likely to adequately balance clinical outcomes and treatment burden for patients with nAMD.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries, affecting up to 18% of adults aged over 85 years.[1–5] Without treatment, the progressive loss of central visual acuity (VA) that characterises late-stage AMD leads to severe and permanent visual impairment and legal blindness. This can have a major impact on patients' quality of life, ability to perform day-to-day activities and functional independence, contributing to considerable emotional impact.[5–8] Delay in initiating nAMD treatment and poor patient adherence can contribute to suboptimal outcomes, highlighting the need for management approaches that incorporate timely and effective treatment at intervals to match the needs of each patient.[9 10] Prior to the early 2000s, treatment options for neovascular AMD (nAMD) were limited to laser photocoagulation and photodynamic therapy (PDT), but these are now redundant in current clinical practice in the context of newer treatment options because of the relatively poor visual outcomes and risk of adverse events.[10–13]

Confirmation that vascular endothelial growth factor (VEGF) is a key pathogenic factor in the development of nAMD[12] was a milestone that subsequently led to highly effective, novel anti-VEGF therapies (including the RNA oligonucleotide, pegaptanib and particularly the anti-VEGF monoclonal antibodies, ranibizumab and intravitreal aflibercept).[10 11 13–17] Ranibizumab, first approved in 2006, prevented vision loss and led to gains in VA compared with either PDT or sham injections in two key phase III clinical trials, ANCHOR and MARINA, with monthly intravitreal injections.[15 16] Intravitreal aflibercept, a soluble decoy VEGF receptor,[18] was approved in 2011 for the treatment of nAMD as a result of significant VA gains in the phase III VIEW 1 and 2 trials, using a regimen of three initial monthly injections followed by injections every 8 weeks in Year 1 and every 12 weeks or more in Year 2 and beyond, based on visual/anatomical outcomes evaluated monthly.[13 19 20]

Although randomised controlled trials (RCTs) such as ANCHOR, MARINA and VIEW are considered the 'gold standard' for establishing efficacy and safety, their relevance to real-life clinical practice is restricted by the selective trial populations and controlled environment.[21] Real-world evidence (RWE) generated in clinical practice can offer additional insights into the effectiveness, safety and practicality of treatments in heterogeneous patient populations, and can highlight the influence of treatment patterns on real-world adherence, persistence and outcomes.[10 21]

The aim of this article is to evaluate the contribution of RWE in changing treatment practices with anti-VEGF therapy in nAMD and to examine its role in optimising anti-VEGF treatment regimens to maintain the best long-term visual outcomes for patients, while reducing the burden of therapy.

METHODS

This narrative review was informed by a structured literature search to include evidence in an unbiased manner. A search of the PubMed database was performed on 5 July 2018, using the following search terms: (long-term OR real-life OR longitudinal OR cohort OR clinical experience OR open-label OR real-world OR database OR non-interventional OR observational) NOT (randomised OR randomised OR tumour OR tumour) AND (ranibizumab OR Lucentis OR aflibercept OR Eylea OR bevacizumab OR Avastin) AND age-related macular degeneration

NOT (Review[ptyp]) NOT diabetic macular oedema, and was limited to English language. The literature search results were reviewed, and relevant articles identified based on their titles. For any articles where the relevance was unclear, abstracts and full manuscripts were reviewed to ensure that data regarding long-term VA and treatment regimens over 12-month periods were included. Additionally, reference lists from studies identified during the literature search were reviewed and any further relevant articles and conference abstracts were included (online supplemental tables 1 and 2 provide a full summary of relevant data from the identified literature).

Articles identified during the literature search were selected for discussion in this review based on the relevance to changes in clinical practice and weight of the evidence described. As such, this review is intended to provide a narrative description of the evolutions of treatment paradigms in nAMD, rather than serve as a systematic summary of all available data on the topic.

To support analysis of the outcomes reported in the identified articles, and place the findings in the context of the current nAMD landscape, two further papers were considered, which report comparisons between data for current anti-VEGF therapies and those in development[22] and RWE from nearly 50 000 eyes with nAMD.[23]

RESULTS

Since the approval of ranibizumab and intravitreal aflibercept for the treatment of nAMD, a growing body of evidence has demonstrated the real-world effectiveness of anti-VEGF therapy, supporting the optimisation of treatment regimens.

Anti-VEGF treatment in pro re nata (PRN; as needed) regimens

The initial approval of ranibizumab in a fixed monthly regimen was based on the phase III ANCHOR and MARINA trials that enrolled >1000 patients and demonstrated gains in VA of +7.2 and +11.3 letters after 1 year with 0.5 mg ranibizumab monthly dosing.[15 16] However, the requirement for monthly dosing was associated with a high treatment burden for patients and healthcare systems, resulting in difficulty adhering to treatment in real-world settings and driving the move towards PRN regimens.[24] With PRN treatment, patients are monitored frequently (typically monthly), but only treated when disease reactivation, or worsening, is detected (decrease in VA and/or anatomical outcomes as measured by optical coherence tomography or fluorescein angiography).[10] PRN regimens may be initiated after initial fixed doses have achieved maximum VA gains and disease stability.[20 25]

Subsequent RCTs evaluated the efficacy of PRN regimens compared with monthly injections for maintaining VA gains, with the aim of reducing treatment burden.[26 27] The largest were the phase III CATT and HARBOR trials, in which clinically meaningful increases in VA were observed after 12 months of ranibizumab PRN treatment (+6.8 and +8.2 letters, respectively). However, these findings were statistically non-inferior to the letter changes in the monthly dosing arms in the CATT trial, and did not reach the prespecified non-inferiority comparison in the HARBOR trial (+8.5 and +10.1 letters, respectively).[26 28] Since initial approval, the ranibizumab label has been updated to monthly injections initially, until maximum VA is achieved and/or there are no signs of disease activity, followed by PRN with monitoring and injections at the physician's discretion, based on disease activity. The ranibizumab label also provides guidance on use as part of a treat-and-extend (T&E) regimen and, once maximum VA is achieved and/or there are no signs of disease activity, treatment intervals can be extended stepwise (by no more than 2 weeks at a time for nAMD) until signs of disease activity or visual impairment recur.[25]

The 62 publications describing outcomes of anti-VEGF PRN regimens in routine clinical practice are outlined in online supplemental table 1. Of note, two meta-analyses examining the effectiveness of ranibizumab in real-world studies were identified. Guo *et al* reported an improvement of +4.85 letters after 1 year in 37 observational studies with ranibizumab treatment (which included fixed-dose and PRN regimens).[29] Similarly, Kim *et al* reported an increase of +3.5 letters at Year 1 with ranibizumab PRN regimens (N=20 247); however, this was not maintained, reducing to +1.3 letters at Year 2 and −1.9 letters by Year 3 (N=14 408 and 11 714, respectively).[30]

Three articles reported outcomes for studies including >1000 patients on PRN regimens (AURA, LUMINOUS and IRIS) and, in all, improvements in VA were observed with ranibizumab PRN treatment at 1 year compared with baseline.[31–33] However, in AURA, which continued beyond 1 year of treatment, the initial gains in VA observed after 4 months with initial ranibizumab monthly injections, were not maintained at Year 1 and continued to decline towards the end of Year 2.[31] In studies continuing beyond 3 years, declining VA with anti-VEGF PRN regimens was observed over the long term.[34–42] Furthermore, in a small study in which initial VA gains were maintained for up to 5 years, the number of injections administered annually increased in later years (median of seven injections in Year 5 vs four injections in Years 2–4).[43] This observation is consistent with other studies that indicated that, despite treatment being administered on a PRN basis, a higher number of injections is independently correlated with improved VA for patients with nAMD treated with ranibizumab.[33 44–47]

RWE has highlighted the challenges associated with matching the outcomes observed in RCTs with PRN regimens in routine clinical practice, including physician preference, under-treatment and patient adherence.[10 22 31 32] This drove efforts to investigate alternative anti-VEGF regimens, to maximise and maintain VA gains for all patients.

Fixed bimonthly dosing

Intravitreal aflibercept was initially approved in a bimonthly regimen after three initial loading doses, supported by the phase III VIEW 1 and 2 trials, in which similar mean gains in VA were observed with 4-weekly and 8-weekly dosing (9.3 letter gain with 4-weekly dosing and 8.4 with 8-weekly dosing of intravitreal aflibercept 2 mg).[19]

Nine articles describing outcomes of bimonthly fixed-dose anti-VEGF regimens in routine clinical practice were identified, all of which investigated the effectiveness of intravitreal aflibercept in a bimonthly dosing regimen following three initial loading doses (online supplemental table 1). No RWE on the effectiveness of fixed bimonthly dosing with ranibizumab was identified.

Regardless of study type, intravitreal aflibercept administered in a bimonthly regimen following three initial monthly doses was consistently associated with gains in VA at Year 1, with improvements in vision ranging from +3.0 to +8.0 letters from baseline.[48–56] Talks *et al* concluded that the VA gains observed were comparable to those reported in the VIEW 1 and 2 phase III trials.[48]

Several real-world studies have compared the effectiveness of intravitreal aflibercept bimonthly treatment with intravitreal aflibercept and ranibizumab PRN regimens. In PERSEUS, when both treatment-naïve and -experienced patients were considered, those receiving regular bimonthly intravitreal aflibercept achieved significantly

greater improvements in VA than those in the irregular treatment cohort (+6.1 letters vs +1.5 letters, respectively, at Year 1; p=0.008).[49] Similar observations were made in the RAINBOW study; however, in both studies, the irregular cohorts did not have a strict definition and, although a PRN regimen was assumed by the authors, the number of injections was lower than is recommended by EURETINA guidelines.[13 49 56] In a retrospective analysis of electronic medical records in the UK, patients receiving intravitreal aflibercept (initial loading doses followed by fixed bimonthly dosing) achieved gains of +5.93 letters at Year 1, compared with +2.55 letters for those receiving ranibizumab (initial loading doses, then PRN), despite lower baseline VA for patients initiating ranibizumab.[57]

The effectiveness of fixed bimonthly dosing has been demonstrated in routine clinical practice, with evidence indicating improved outcomes compared with PRN regimens. However, fixed treatment is still associated with considerable treatment burden.[10 48–56]

T&E regimens

T&E regimens aim to personalise treatment, further reducing the burden on patients and healthcare systems, by allowing variation in treatment interval based on the individual patient's disease activity, while optimising anti-VEGF efficacy compared with PRN regimens. Although specific dosing schedules may vary according to drug, after initial loading doses, T&E regimens typically involve treatment administration at every scheduled clinic visit, with incremental increase or decrease in the interval between each visit according to anatomic outcomes and VA—the objective being to maximise the interval between injections without disease recurrence.[10 20 25]

RCTs have demonstrated good visual outcomes for patients receiving T&E regimens with anti-VEGF therapies. T&E regimens with ranibizumab were shown to be non-inferior to monthly dosing in the phase III TREND and TREX-AMD RCTs, with +6.2 vs +8.1 letter in TREND (Year 1) and +8.7 vs +10.5 letter in TREX (Year 2) gains, respectively.[58 59] Similarly, the second year of the phase III RCTs, VIEW 1 and 2, and the 2-year prospective, open-label ATLAS study provided evidence for the ability to extend intravitreal aflibercept beyond bimonthly dosing to 12-week intervals.[60 61] Patients receiving intravitreal aflibercept in a T&E regimen in the RCT ALTAIR achieved gains in VA of +9.0 and +8.4 letters at Year 1 for 2-week and 4-week adjustment periods, respectively.[62]

Twenty-five articles describing outcomes with T&E regimens with ranibizumab, intravitreal aflibercept and bevacizumab in routine clinical practice were identified (online supplemental table 2). Although T&E dosing, according to the aflibercept label, was not strictly adhered to in all studies, together, they confirm that a real-world, T&E protocol with anti-VEGFs can improve VA over periods of up to 3 years in patients with nAMD.[50 61 63–78]

Meta-analyses have supported initial observations that better visual outcomes are achieved with T&E regimens while reducing the burden on patients, clinics and physicians.[30] Furthermore, a meta-analysis of four studies comparing PRN, T&E and fixed monthly dosing with ranibizumab indicated that T&E dosing offers similar visual outcomes to monthly dosing, while reducing injection burden.[79] In contrast, improvements in VA over 12 months were significantly lower with PRN dosing than with a T&E regimen.[79]

It is important to note that while good visual outcomes can be achieved with extended injection intervals, recent findings indicate that there is a positive and clinically meaningful correlation between the number of injections and VA outcomes[22] and that injection frequency in the first year is an important contributor to VA gains.[22 23]

Initial loading doses

Regardless of treatment regimen, RWE has demonstrated the importance of receiving initial loading doses for achieving optimal outcomes for patients with nAMD. Typically, gains in VA are observed in the first 3 months of treatment with initial loading doses, and the aim of subsequent treatment (regardless of regimen) is to maximise and maintain initial gains.[80] In the large, observational RAINBOW study, treatment-naïve patients receiving full initial intravitreal aflibercept loading doses achieved significant gains in VA compared with baseline at Year 1, with no improvement in those who did not receive the initial loading doses (+7.1 letters in regular cohort vs −1.1 letters in irregular cohort who did not receive initial loading doses, at 12 months).[56]

DISCUSSION

The discovery of anti-VEGF therapies led to a paradigm shift in the management of nAMD, as these became the first treatment option associated with improvements in VA in RCTs.[15 16] Since their initial approval, anti-VEGF treatment regimens have been adapted by physicians to meet patients' needs and healthcare resource availability. Regimens have evolved in parallel with emerging RWE, with the aim of optimising visual outcomes and reducing treatment burden. Here, we identify and describe the growing body of evidence supporting the effectiveness of anti-VEGF therapy for the treatment of nAMD in routine clinical practice.

Initial fixed monthly ranibizumab regimens were associated with good efficacy and tolerability in RCTs.[15 16] However, these outcomes were not mirrored in early real-world studies due to under-treatment resulting from treatment burden. PRN regimens offered the opportunity to achieve visual gains at Year 1, with a reduced number of injections, but visual outcomes were suboptimal and monthly appointments were required, even when an injection was not needed, which compromised the reduction in treatment burden.[29 30] In contrast, intravitreal aflibercept in a bimonthly regimen after three initial loading doses was associated with good visual outcomes and tolerability in both RCTs and real-world studies.[19 48–56]

The opportunity to reduce patient, physician and clinic burden and optimise visual outcomes, led to the investigation of anti-VEGF T&E regimens. Recently, a growing body of evidence has emerged from RCTs and real-world studies supporting the effectiveness of T&E regimens with anti-VEGFs.[58 62 81] Evidence so far indicates that T&E regimens are associated with improved visual outcomes compared with PRN regimens at Year 1 and beyond, with potentially fewer clinic visits than fixed monthly or PRN dosing.[30 79] These findings demonstrate the clinical and quality of life benefits T&E regimens offer to patients, clinics and physicians, compared with PRN regimens.

Our comprehensive review included more than 100 articles describing treatment regimens and outcomes with anti-VEGF treatment for nAMD in real-world clinical practice and reflects the currently available body of evidence. A limitation to the analysis may arise from heterogeneity in the methods and populations of the included studies, and the relatively small sample size and retrospective nature of many of the studies, which may make generalisation inappropriate and limit definitive comparisons. Although a number of network meta-analyses have been conducted using clinical trial data from RCTs to assess the efficacy and safety of anti-VEGF treatments,[82 83] the present literature review differs in that it offers insights into the use of anti-VEGF treatment of nAMD in a real-world setting and how RWE has actively informed new, pragmatic, treatment strategies.

In conclusion, RWE has helped to shape and improve treatment strategies in nAMD in clinical practice, and demonstrates that T&E regimens can optimise visual outcomes and reduce treatment burden for patients with nAMD.

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