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REVIEW

Twelve-week dosing with Aflibercept in the treatment of neovascular age-related macular degeneration

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Purpose: To review published evidence for a treatment interval extension to ≥12-weeks in neovascular macular degeneration treated with intravitreal Aflibercept.

Methods: A systematic search was performed in the NCBI/PubMed database to identify pro- and retrospective studies retrieved by the key terms <exudative> or <neovascular> and <AMD> or <age-related macular degeneration> AND <intravitreal therapy> AND <Aflibercept> and included all papers that used a treat-and-extend (T&E) protocol including a loading phase of 3 intravitreal anti-VEGF injections and a minimal follow-up of 2 years. Disease stability was defined as the absence of any intraocular and absence or stability of subretinal fluid and pigment-epithelial detachment.

Results: Four studies were identified that reported information pertaining to disease stability or treatment extension beyond 12 weeks under intravitreal Aflibercept therapy including 1,102 eyes in total. Following a T&E protocol, a mean of 62.9% achieved disease stability and a 6.9 letter gain based on 11.9 injections over 24 months of Aflibercept treatment. As much as 43.0% of all eyes or 64.1% of the eyes with stable disease were maintained on ≥12-weekly injection intervals.

Conclusions: A consequent treatment with a null tolerance for intraretinal fluid is prerequisite to induce stability and maintain visual gain after the loading phase. Using Aflibercept in a T&E protocol, disease stability and interval extension to ≥12 weeks were reported in 43% of the eyes by end of the second year with less injections, but similar results as under fix dosing. A lower treatment burden strongly argues for an individualized proactive treatment regimen.

Keywords: neovascular age-related macular degeneration, AMD, Aflibercept, intravitreal anti-VEGF injections, treat-and-extend, proactive treatment, long-term outcome, review

Introduction

Monthly treatment of exudative or neovascular age-related macular degeneration (nAMD) with intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents typically goes along with an impressive short-term effect,[1–3] if treated before neuroretinal atrophy and subretinal fibrosis have developed.[4,5] This gain is, however, lost over the following years after the patients have been switched to an as needed or pro re nata (PRN) therapy.[6–9] Compared to randomized clinical trials (RCTs), the initial visual gain is less pronounced whereas the mid- to long-term vision loss is more pronounced in real life because exclusion criteria or negative predictors for vision gain in RCTs such as subfoveal fibrosis or hemorrhage and systemic comorbidities limiting a regular access to treatment do not apply to real life.[10–12] Obviously, functional stability in real

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life is related to regular clinical visits and the number of intravitreal injections[13,14] as well as the individual response to treatment with 50% of the patients newly developing disease activity despite monthly intravitreal ranibizumab therapy.[15]

With the introduction of Aflibercept for the treatment of nAMD in late 2012,[3] the discussion focused on the quality of response,[16–18] terms such as insufficient response and treatment resistance were defined and used as reason for switching from one to the other therapy.[19,20] This indicates a shift in the aim of treatment from prevention of a severe vision loss for a previously blinding disease[21,22] to long-term disease stability which is only achieved in the absence of any intraretinal and stability of subretinal fluid and/or pigment-epithelial detachment.

Since the potential visual gain and safety outcomes were similar between prospective studies with different anti-VEGF agents,[16,23] the burden of disease and its treatment for patients and caregivers became central[24–26] and the number of visits and injections the most critical marker for treatment success.[27–31]

Real-life data pertaining to the long-term stability under treatment with Aflibercept beyond two to three years are still scarce,[32–35] and few papers addressed predictive factors for long-term functional stability.[36–41] Clinical experience has taught that independent of the anti-VEGF drug in use, the PRN treatment strategy in RCTs and clinical practice has an inherent risk of undertreatment since lesion activity indicated by intraretinal fluid triggers re-treatment. This results in progression of subretinal fibrosis and finally loss of vision in nAMD,[10,11,42] whereas the risk of progression of geographic atrophy in response to over-treatment seems relatively low.[41] Consequently, good responders maintaining a dry macula with less than an injection every 2 months did not meet major interest[43] until recently, when the 12-month results from 2 new prospective randomized clinical trials (Harrier and Hawk)[44] comparing the effects of the investigational drug Brolucizumab to Aflibercept indicated that the portion of eyes that demonstrated a complete resolution of intraretinal fluid was higher under the former therapy allowing a treatment extension to 12 weeks in half of the patients[44] whereas Aflibercept was delivered per label at a fix dosing every 2 months. The underlying review therefore presents an overview of the few published data on treatment extension of Aflibercept to 12 or more weeks and possible predictors of this low treatment demand.

Patients and methods

A systematic search was performed in the NCBI/PubMed database from the National Institute of Health, USA (https://www.ncbi.nlm.nih.gov/pubmed), to identify pro- and retrospective studies retrieved by the key terms <exudative> or <neovascular> and <AMD> or <age-related macular degeneration> AND <intravitreal therapy> AND <anti-VEGF> or Ranibizumab> or <Aflibercept>. Based on this set of manuscripts, all abstracts were selected that had been published in the last 10 years (since 2008), used a loading phase of 3 intravitreal Aflibercept injections (2mg/50ul) and a minimal follow-up of 2 years. Case reports and series with less than 50 patients were excluded, whereas cross-references identified during the literature search were included if they provided new information. For the purpose of this review, disease stability was defined as the absence of any intraretinal and absence or stability of subretinal fluid and pigment-epithelial detachment while data pertaining to the change in lesion size were not found.

Results

A total of four studies, one randomized clinical trial and three real-life studies, reported information pertaining to treatment extension beyond 12 weeks under intravitreal Aflibercept therapy. Following a T&E protocol, disease stability was achieved in 62.9% (50.1–92.0) of 1,102 eyes, and 43.0% (24.0–52.8) of eyes reached ≥12-weekly injection intervals (Table 1).[9,33,35,45] Because the corresponding RCT and real-world clinical studies did not use comparable outcome measures and identical treatment regimes, an evidence-based analysis of prognostic markers is not available, but few prognostic factors have consistently been reported in the different studies for disease stability, beyond these patient age, duration between first symptoms and treatment initiation, lesion size, absence or presence of intraretinal fluid after end of the loading phase and after 12 months, and the number of injections needed during the first year under an individualized therapy. A presenting visual acuity below 70 letters (20/40) resulted in a larger visual gain, but a lower final visual acuity than a visual acuity of ≥70 letters.[46–49]

Discussion

Clinical experience[20,50] and the aforementioned head-to-head studies indicate that approximately half of the eyes respond equally well to Ranibizumab and Aflibercept treatment,[51]

Table 1 Overview of published data

Reference	46	47	33	35	Together
Authors	Richard[a]	Barthelmes	Eleftheriadou	Traine	
Year of publication	2015	2018	2018	2019	2015–19
Study design	P	R	R	R	
n (eyes)	511	212	148	231	1,102
Patient retention over 24 months (%)	84.0	64.2	83.8	80.0	78.0
VA gain (12 months)[b]	9.8	n.r.	5.9	5.7	7.1
VA gain (24 months)[b]	9.5	6.0	6.4	5.7	6.9
Injections in year 1 (n)	7.5	7.0	7.2	7.7	7.4
Injections in year 2 (n)	3.0	5.8	4.6	4.4	4.5
Disease stability by end of year 2 (%)	50.1	92.0	57.3	52.0	62.9
Treatment intervals ≥12-weeks in year 2 (%)	48.3	24.0	52.8	46.9	43.0

Notes: [a]The VIEW 1 and 2 studies used a "capped PRN" approach for the 2q8 group: bimonthly Aflibercept injection after the loading phase in year one; patients that had achieved disease stability by then proceeded under a mandatory proactive treatment every 12 weeks as long as no disease activity was detected9 [b]ETDRS letters.
Abbreviations: P, prospective; R, retrospective real-life, n.r., not reported.

indicating that these eyes might maintain functional and morphological stability of their exudative age-related macular degeneration (AMD) with a less intensive treatment[35,51] than fix anti-VEGF dosing which was monthly for Ranibizumab or bi-monthly for Aflibercept in the VIEW studies.[51,52] The dry AMD component, the involutive process of the retinal pigment epithelium and choriocapillaris, will progress independently in the long term, lately resulting in vision loss despite anti-exudative therapy.[11,41,42] Nevertheless, 98% of the eyes with early nAMD indicated by a good presenting best-corrected visual acuity (BCVA; 70 ETDRS letters or driving vision) will maintain their function over 2 years despite a reduced number of injections in the second year according to the individual treatment demand.[45] This is owed to a shift from a reactive to a proactive re-treatment strategy using not only functional but also anatomic disease activity criteria, namely intraretinal fluid on OCT.[43] A good early functional response may, however, precede the anatomic response and go along with excellent long-term functional results: Attaining a satisfying functional 3-year outcome was closer (OR 9.8) correlated to a BCVA of ≥70 compared to <70 letters than to absence or presence of lesion activity (OR 1.6) by end of the loading phase following a treat-and-extend protocol.[49] This is supported by another recently published study which found that independent of the number of injections, eyes with good initial BCVA had a good functional outcome over up to 4 years whereas eyes with poor initial BCVA despite a good initial visual gain deteriorated during the follow-up which was associated to the presence of intra- and subretinal fluid and subretinal fibrosis.[48] Today, virtually no retina expert would delay intravitreal treatment in nAMD until a five-letter loss of vision despite the presence of intra- or subretinal fluid. A vision loss of ≥5 letters (1 line) was postulated as a re-treatment criterion for most prospective studies by the FDA and EMA. And likewise, virtually nobody would nowadays judge treatment necessary in the absence of any disease activity (no intra- or subretinal fluid on OCT) because of a five-letter loss.[43,53] The OCTAVE study, designed to compare the sensitivity of a BCVA-driven to a combined BCVA/OCT-driven re-treatment, was terminated early because it had become evident by then that a re-treatment decision driven by morphological parameters adding to BCVA results in better macular long-term stability (Staurenghi G, personal communication, March 2019).

Both eyes of an individual must not respond similarly to treatment.[54–56] Usually, the second eye is treated earlier resulting in a better long-term outcome.[57] Several factors independent of the anti-VEGF drug in use and disease activity are related to the response to treatment, which is

beyond the scope of this review.[28,37,48,56–60] To summarize these studies, the portion of eyes achieving a good BCVA (≥70 compared), a complete absence of any intra- and subretinal fluid by end of the first and second year of treatment and allowing a treatment extension to 12 or more weeks after 1 and 2 years may become more relevant as markers of treatment efficacy.[44,49] According to these parameters, approximately half of the eyes in the VIEW studies achieved stability in the second year under a capped PRN (reactive treatment on an as-needed basis for all eyes presenting disease activity, and a complimentary proactive Aflibercept treatment every 12 weeks in eyes with a stable functional and morphological situation), whereas the other half of still active lesions and treated as needed lost 5 letters.[9] In a recently published large real-life cohort study, on the other hand, 82% of the eyes became inactive within the first year after a median time of only 71 days and 3 intravitreal Aflibercept injections,[9] respectively, which meets well with preclinical pharmacological data.[61,62] A visual gain of +3.9 letters at 24 months of follow-up was encountered under a treat-and-extend protocol while the portion of eyes requiring an Aflibercept injection at an interval of longer than 10 weeks was only 24%[45] which is half of the portion reported by other studies.[35,51] The remarkable differences with regard to achieving disease stability and treatment extension to ≥12 weeks between the single studies indicate obviously a large inter-individual variability in the treatment demand and the presence of other impact factors such as lesion size, visual acuity at diagnosis and duration of symptoms until treatment initiation which may have to be taken into account.[47,63–65] Only a consequent suppression of lesion activity will result in a 10-letter or two-line better 2-year outcome using a treat-and-extend protocol[9,35,45] than reported with the "capped PRN arm" with a loss of 3.1–3.8 letters in the VIEW study.[9] Interestingly, 47.6% of the eyes in the "capped PRN arm" in VIEW 1 and 2 achieved disease stability by end of year 1 qualifying them for a proactive treatment every 12 weeks. These eyes widely maintained the vision gain encountered by the end of year 1 (−0.6 letters; Table 1).

The favorable outcomes of a null-tolerance against intraretinal fluid, moreover, have recently received support from prospective clinical trial, the Altair study.[66] According to the interim analysis of the as yet not fully published study in a Japanese population under a treat-and-extend regimen, the Aflibercept treatment interval was extended to 12 weeks in 42.3% (2-week treatment extension arm) to 49.6% (4-week extension arm) by week 52,[66] and 62.1–62.7% of the eyes experienced a treatment interval extension to 12 weeks and a visual gain of 6.1 and 7.6 ETDRS letters by week 96.[67] In response to such favorable outcomes, the US FDA has recently approved a change of the treatment label allowing a treatment interval extension up to 12 weeks for Aflibercept.

In conclusion, consequently following a treat-and-extend protocol using Aflibercept treatment according to individual needs was reported to result in morphological and functional stability in two-thirds of eyes after 2 years and allows a treatment interval extension to ≥12 weeks in 43% of the eyes based on a patient retention of 78% indicating a high patient satisfaction with this protocol.

Disclosure

JGG acts as an advisor for several pharmaceutical companies (AbbVie, Alcon, Allergan, Bayer, Novartis) and contributes to several international industry-sponsored clinical studies. The underlying manuscript is independent of these activities. The author received no direct or indirect support for this study nor has he conflicting interests with the data that are presented herein. The author reports no other conflicts of interest in this work.

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