Drugs Aging (2012) 29:839–846
DOI 10.1007/s40266-012-0015-2

ADIS DRUG PROFILE

# Aflibercept for Intravitreal Injection

## In Neovascular Age-Related Macular Degeneration

**James E. Frampton**

Published online: 5 October 2012


**Abstract** Aflibercept is a recombinant human fusion protein that acts as a soluble decoy receptor for vascular endothelial growth factor (VEGF) family members VEGF-A, VEGF-B and placental growth factor, thereby preventing these ligands from binding to, and activating, their cognate receptors. The efficacy of intravitreal aflibercept in the treatment of wet (neovascular) age-related macular degeneration has been compared with that of intravitreal ranibizumab, the current gold standard for this indication, in two pivotal phase III studies of virtually identical design (VIEW 1 and 2). In both trials, the recommended regimen of aflibercept [2 mg every second month (after three initial monthly doses)] was shown to be noninferior to the recommended regimen of ranibizumab (0.5 mg every month) in terms of the primary endpoint of the proportion of patients who maintained their vision after 1 year of treatment; similar results were seen when monthly dosing with aflibercept (0.5 or 2 mg) was compared with ranibizumab. Over a period of 96 weeks in the VIEW studies, patients receiving the recommended regimen of aflibercept during the first year followed by modified quarterly treatment during the second year had a similar visual acuity gain to those receiving the recommended regimen of ranibizumab during first year followed by modified quarterly treatment during the second year, but on average required five fewer injections. Aflibercept was generally well tolerated in the VIEW studies; the ocular and non-ocular adverse event profile of the drug was similar to that of ranibizumab.

**Features and properties of aflibercept (EYLEA™)**

| | |
|---|---|
| **Indication** | |
| Wet (neovascular) age-related macular degeneration | |
| **Mechanism of action** | |
| Neutralizes vascular endothelial growth factor (VEGF) family members VEGF-A, -B and placental growth factor | |
| **Dosage and administration** | |
| Dose | 2 mg per (affected) eye |
| Route of administration | Intravitreal injection |
| Frequency of administration | Every month (4 weeks) for the first 3 months followed by every 2 months (8 weeks) |
| **Mean pharmacokinetic parameters for free aflibercept (following repeated intravitreal injections of aflibercept 2 mg/eye)** | |
| Mean maximum plasma concentration ($C_{max}$) | 0.02 mg/L |
| Area under the plasma concentration-time curve from time zero to the time of the last measurable concentration | 0.15 mg · day/L |
| Time to $C_{max}$ | 1–3 days |
| **Most common (incidence ≥5 %) treatment-emergent ocular adverse events** | |
| Conjunctival haemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters and increased intraocular pressure | |

**The manuscript was reviewed by:** D.A. Boyer, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; M. W. Stewart, Department of Ophthalmology, Mayo Clinic Florida, Jacksonville, FL, USA.

J. E. Frampton (✉)
Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore, 0754 Auckland, New Zealand
e-mail: DRA@adis.com

## 1 Introduction

If left untreated, or inadequately treated, age-related macular degeneration (AMD), is the leading cause of irreversible vision loss among older adults in Western countries [1, 2]. In the US, the number of people with

AMD is predicted to rise from 1.75 million in 2000 to 2.95 million in 2020 [1]. The early form of the disease is characterized by the presence of macular drusen with or without changes in the retinal pigment epithelium (RPE), while the late stage encompasses both dry AMD, which is characterized by atrophy of the RPE, and wet (neovascular) AMD, which is characterized by choroidal neovascularization (CNV) and/or RPE detachment [3, 4]. Neovascular AMD only constitutes a minority of AMD cases (10–15 %); however, it accounts for most of the severe vision loss due to the disease (90 % of cases) [1, 5, 6].

The vascular endothelial growth factor (VEGF) family and its receptors are essential regulators of angiogenesis and vascular permeability [7, 8]. The VEGF family member VEGF-A plays a central role in the development of CNV, which is the underlying cause of vision loss in patients with neovascular AMD; this has led to intravitreal anti-VEGF therapies that selectively inhibit VEGF-A being investigated for the treatment of the disease [1, 6]. Pegaptanib, an aptamer that specifically binds to, and blocks, the VEGF-A165 isoform [9], and ranibizumab, a humanized, monoclonal antibody fragment that binds to, and inhibits, multiple VEGF-A isoforms [10, 11], are two such agents that have been approved for the treatment of neovascular AMD in the US; ranibizumab is considered to be the current gold standard for this indication [1]. Bevacizumab, a full-length, humanized, monoclonal antibody, is a third such agent; it is commonly used in the US, despite not being approved by the US FDA for the treatment of neovascular AMD [12]. Intravitreally administered anti-VEGF therapies have improved outcomes compared with previous therapies for neovascular AMD; in the case of ranibizumab and bevacizumab, individualized treatment regimens aimed in part at minimizing the frequency (and associated risks) of injections have emerged as alternatives to traditional monthly dosing [13].

Aflibercept (EYLEA™; also known as 'VEGF Trap-Eye') [14, 15] is an intravitreally administered anti-VEGF agent that binds to, and thereby neutralizes, all VEGF-A isoforms. In addition, unlike ranibizumab or bevacizumab, it neutralizes two other VEGF family members (ligands), namely VEGF-B and placental growth factor (PlGF), that have also been implicated in pathological vascular remodelling [16]. Experimental evidence shows that targeting VEGF-B [17] and PlGF [18] inhibits CNV and suggests that PlGF synergizes with VEGF-A in promoting vascular pathology in neovascular AMD [16]. To date, aflibercept has been approved for the treatment of neovascular AMD in the US [19] and Australia [20].

This article reviews the efficacy and tolerability of aflibercept in the treatment of patients with neovascular AMD, and summarizes its pharmacological properties. Medical literature (including published and unpublished data) on the use of aflibercept in neovascular AMD was identified by searching databases for studies published since 1996 (including MEDLINE and EMBASE), bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug. Searches were last updated 17 September 2012.

## 2 Pharmacodynamic Profile

Aflibercept is a fully human, soluble, recombinant decoy VEGF receptor (or 'VEGF-Trap'). It consists of the second extracellular binding domain of VEGF receptor-1 (VEGFR-1) and the third extracellular binding domain of VEGF receptor-2 (VEGFR-2) fused to the Fc portion of immunoglobulin G1 [21, 22].

In vitro, aflibercept binds with high affinity to VEGF-A [dissociation constant ($K_d$) of 0.36 and 0.49 pmol/L for the human VEGF-$A_{121}$ and $A_{165}$ isoforms, respectively] [16, 23]. Because aflibercept binds VEGF-A with higher affinity than both VEGFR-1 ($K_d$ of 9.33 pmol/L for human VEGF-$A_{165}$) [16] and -2 ($K_d$ of 88.8 pmol/L for human VEGF-$A_{165}$) [16], it effectively prevents the binding of VEGF-A to, and the activation of, its cognate receptors [24]. Aflibercept forms a stable, inert 1:1 complex with the VEGF-A ligand [25].

The binding affinity of aflibercept for human VEGF-$A_{165}$ was substantially ($\approx$100-fold) higher than that of ranibizumab ($K_d$ of 46 pmol/L) and bevacizumab ($K_d$ of 58 pmol/L), as assessed under identical experimental conditions. This was primarily attributed to the association rate constant ($K_a$) for aflibercept binding to human VEGF-$A_{165}$, which was 256 and 77 times faster than the corresponding $K_a$ values for ranibizumab and bevacizumab, respectively [16].

Aflibercept also binds with high affinity to VEGF-B ($K_d$ of 1.92 pmol/L for the truncated amino acid 10–108 form of human VEGF-B) and PlGF ($K_d$ of 392.0 and 38.9 pmol/L for the human PlGF-1 and -2 isoforms, respectively) [16, 23]. In contrast, neither ranibizumab nor bevacizumab bind to human PlGF-2 [16]. In a similar fashion to that described for VEGF, aflibercept forms a stable, inert 1:1 complex with the PlGF ligand [25], thereby inhibiting the activity of the latter at VEGFR-1 receptors [26].

In vitro, aflibercept was more potent than ranibizumab and bevacizumab in blocking VEGF-A induced activation of VEGFR-1 and -2, and also in inhibiting VEGF-A-induced human umbilical vein endothelial cell (HUVEC) migration. Additionally, aflibercept blocked both PlGF-mediated activation of VEGFR-1 and PlGF-induced HUVEC migration,

whereas ranibizumab and bevacizumab showed no such activity [16].

Intravitreally administered aflibercept inhibited CNV in animal models of laser-induced CNV [27, 28]. In particular, aflibercept both prevented the development of new lesions and caused regression of established lesions in non-human primate models of laser-induced CNV [27].

Intravitreal injections of aflibercept (0.05, 0.15, 0.5, 1, 2 and 4 mg/eye) produced functional and anatomical improvements in a phase I single-ascending-dose study in 21 patients with neovascular AMD [CLinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial (CLEAR-IT 1)] [29]. At 6 weeks post-injection, the increase from baseline in mean best-corrected visual acuity (BCVA) was 4.4 Early Treatment Diabetic Retinopathy Study (ETDRS) letters for all aflibercept dosage groups combined; the decrease from baseline in mean foveal thickness (as determined by optical coherence tomography) was 104.5 μm.

The improvements in functional and anatomical outcomes were largely dose dependent [29]. At week 6, the increases from baseline in mean BCVA were 0.6, 1.2 and 13.5 ETDRS letters in patients receiving a low (0.05, 0.15 or 0.5 mg/eye; $n = 9$), intermediate (1.0 mg/eye; $n = 6$) or high (2 or 4 mg/eye; $n = 6$) dose of aflibercept, respectively; the corresponding decreases from baseline in mean foveal thickness were 57.4, 157.4 and 88.1 μm, respectively.

Of note, three patients who received a high dose of aflibercept experienced significant vision gain (i.e. a gain of ≥15 ETDRS letters); three patients who received a low, intermediate or high dose of aflibercept showed elimination of (CNV-related) fluorescein leakage and a reduction in CNV area [29].

Functional and anatomical outcomes in patients with neovascular AMD who received aflibercept in larger phase III clinical trials are discussed in detail in Sect. 4.

## 3 Pharmacokinetic Profile

The pharmacokinetics of aflibercept have been investigated after intravitreal administration (in phase I–III studies in patients with neovascular AMD) and intravenous administration (in phase I studies in healthy volunteers). The main findings are presented in the US prescribing information [19] and/or the US FDA regulatory review [30].

Following intravitreal injection, aflibercept can be detected in the plasma as free drug (i.e. unbound to circulating endogenous VEGF) or, more predominantly, in the form of a stable, inactive aflibercept:VEGF complex (see Sect. 2) [19, 30].

The mean maximum plasma concentration ($C_{max}$) and area under the plasma concentration-time curve from time zero to the time of the last measurable concentration of free aflibercept were 0.02 (range 0–0.05) μg/mL and 0.15 (range 0–0.59) μg·day/L, respectively, following repeated intravitreal administration of aflibercept 2 mg (per eye) in patients with neovascular AMD; $C_{max}$ was attained in 1–3 days. Free aflibercept was not detectable in the plasma 2 weeks after dosing, nor did it accumulate in the plasma after repeated intravitreal administration of aflibercept at intervals of 4 weeks [19, 30].

Following intravitreal administration of aflibercept 2 mg to patients with neovascular AMD, the mean $C_{max}$ of free aflibercept was estimated to be more than 100-fold lower than the concentration of aflibercept required for half-maximal systemic VEGF binding [19].

The volume of distribution of free aflibercept was ≈6 L following intravenous administration of aflibercept [19, 30].

The metabolism of aflibercept has not been studied; the drug is expected to be eliminated both as a result of binding to free endogenous VEGF and as a result of proteolysis [19, 30]. Free aflibercept is not expected to be eliminated by the kidney, because of its relatively large molecular size (115 kilodaltons) [30].

The terminal elimination half-life of free aflibercept in the plasma was ≈5–6 days following intravenous administration of aflibercept doses of 2–4 mg/kg [19, 30].

Plasma concentrations of free aflibercept or the aflibercept:VEGF complex were not influenced to a clinically significant extent by age, sex or renal function, according to exploratory subgroup analyses from a phase III clinical study [VEGF-trap-eye Investigation of Efficacy and safety in Wet AMD (VIEW) 2; see Sect. 4 for further details] [19, 30].

The US prescribing information [19] indicates that aflibercept dose adjustment based on renal impairment is not needed; however, it does not include a (similar) recommendation regarding hepatic impairment [19]. As is the case with renal impairment, there is no pharmacokinetic basis for dose adjustment based on hepatic impairment [30].

Aflibercept is not expected to interact with other medications; no in vivo drug–drug interactions studies have been conducted (or are needed) [30].

## 4 Therapeutic Efficacy

The efficacy of repeated intravitreal administration of aflibercept in the treatment of neovascular AMD has been compared with that of intravitreal ranibizumab in two pivotal phase III noninferiority studies of virtually identical design (VIEW 1 [31] and 2 [32]; see Table 1 for trial eligibility criteria and patient baseline characteristics).

**Table 1** Randomized, double-masked, multicentre VIEW 1 [31] and 2 [32] studies: eligibility criteria and baseline patient characteristics

| | | |
|---|---|---|
| Key inclusion criteria | | |
| Aged ≥50 years; subfoveal CNV secondary to AMD; ETDRS BCVA letter score of 73–25 (Snellen equivalent 20/40–20/320) | | |
| Key exclusion criteria | | |
| Vitreous haemorrhage in preceding 4 weeks; scarring, fibrosis or atrophy involving the foveal centre; total lesion size >12 disc areas (30.5 $mm^2$); any prior ocular (in the study eye) or systemic treatment or surgery for AMD | | |
| Baseline pt and disease characteristics | VIEW 1 ($n = 1215$)[a] | VIEW 2 ($n = 1202$)[b] |
| Age (years)[c] | 78.0 | 73.9 |
| Sex (% female) | 58.8 | 55.5 |
| Predominantly classic CNV (% pts) | 26.5 | 25.8 |
| Minimally classic CNV (% pts) | 34.1 | 35.4 |
| Occult CNV (%) | 38.3 | 38.4 |
| Total lesion area ($mm^2$)[c] | 6.95 | 8.28 |
| CNV area ($mm^2$)[c] | 6.54 | 7.83 |
| BCVA (ETDRS letters)[c] | 55.1 | 52.4 |
| NEI VFQ-25 total score[d] | 70.7 | 72.1 |

*AMD* age-related macular degeneration, *BCVA* best-corrected visual acuity, *CNV* choroidal neovascularization, *ETDRS* Early Treatment Diabetic Retinopathy Study, *NEI VFQ-25* National eye institute visual function questionnaire, *pt(s)* patient(s)

[a] Safety analysis set; each pt contributed one eye to the study

[b] Full analysis set; each pt contributed one eye to the study

[c] Mean

[d] On a scale of 0 (worst possible) to 100 (best possible)

In the first year of these studies (weeks 0–52), patients were randomly assigned to the recommended dosing regimen of ranibizumab (0.5 mg every 4 weeks) or to one of three different dosing regimens of aflibercept [0.5 mg every 4 weeks; 2 mg every 4 weeks; or 2 mg every 8 weeks (with the first three doses administered at 4-week intervals)] that had previously been identified in a phase II dose- and interval-ranging study in 157 patients with neovascular AMD (CLEAR-IT 2 [24]). The primary endpoint was the proportion of patients who maintained their vision (i.e. lost <15 ETDRS letters) at week 52; secondary endpoints included the proportion of patients who experienced a clinically meaningful improvement in vision (i.e. gained ≥15 ETDRS letters) at week 52 and the mean change from baseline in BCVA at week 52 [19,33–35].

During the second year (weeks 52–96), patients were treated on a modified quarterly basis, i.e. they were assessed monthly and, if necessary, treated (with the same drug and dose as in the first year) no more frequently than every month and no less frequently than every 3 months [33]. This treatment approach has also been referred to as a 'capped pro re nata dosing schedule' [36].

First-year results are available from the US prescribing information [19], conference abstracts (VIEW 1 [34] and 2 [35]) and a press release [33]; second-year results are available from a press release [37].

### 4.1 Year 1 Results

In both trials, all three aflibercept regimens were found to be noninferior to monthly dosing with ranibizumab in terms of the primary endpoint of the proportion of patients who maintained their vision at week 52 (Table 2) [19, 33–35].

Across both trials, ≈95 % of patients receiving aflibercept 2 mg every month or every second month (after treatment initiation with three monthly doses) maintained their vision at week 52, as did ≈95 % of patients receiving ranibizumab 0.5 mg every month (Table 2) [19].

As regards the secondary endpoints, there were no significant differences between the aflibercept and ranibizumab regimens in each trial, with the exception that the mean change from baseline in BCVA at week 52 was greater in the aflibercept 2 mg every month group compared with the ranibizumab group in VIEW 1 [10.9 vs. 8.1 ETDRS letters ($p < 0.01$); Table 2] [19, 33].

Across both trials, patients receiving aflibercept 2 mg every month or every second month (after treatment initiation with three monthly doses) had a mean increase from baseline in BCVA at week 52 that ranged from 7.6 to 10.9 letters; approximately one-third of these individuals (29–38 %) experienced a clinically meaningful improvement in vision (Table 2) [19].

### 4.2 Year 2 Results

In a pooled analysis of the two trials, patients receiving aflibercept 2 mg every second month (after three initial monthly doses) during the first year followed by modified quarterly treatment during the second year had an increase from baseline in mean BCVA of 7.6 letters at week 96, as compared with an increase of 8.4 letters at week 52. They received an average of 11.2 injections over the 96-week period, including 4.2 injections between weeks 52 and 96. Sixteen per cent of patients required frequent (six or more) injections during the second year [37].

In comparison, patients receiving ranibizumab 0.5 mg every month during the first year followed by modified quarterly treatment during the second year had an increase from baseline in mean BCVA of 7.9 letters at week 96, as compared with an increase of 8.7 letters at week 52. They received an average of 16.5 injections over the 96-week period and 4.7 injections between weeks 52 and 96. Approximately one-quarter (26.5 %) of patients required frequent (six or more) injections during the second year [37].

**Table 2** Comparative efficacy of intravitreal aflibercept and ranibizumab for the treatment of neovascular age-related macular degeneration. Summary of results at week 52[a] from two virtually identical, randomized, double-masked, multicentre, phase III trials[b]

| Study | Treatment regimen (mg) [no. of pts] | Efficacy outcome | | |
|---|---|---|---|---|
| | | BCVA maintained[c,d] (% pts) | BCVA improved[d] (% pts) | Mean change from BL in BCVA (EDTRS letters) |
| VIEW 1 | IAI 0.5 q4w [NR] | 96[e] | NR | 8.1 |
| | IAI 2 q4w [304] | 95[e] | 38 | 10.9* |
| | IAI 2 q8w[f] [301] | 94[e] | 31 | 7.9 |
| | RBZ 0.5 q4w [304] | 94 | 31 | 8.1 |
| VIEW 2 | IAI 0.5 q4w [NR] | 96[g] | NR | 9.4 |
| | IAI 2 q4w [309] | 95[g] | 29 | 7.6 |
| | IAI 2 q8w[f] [306] | 95[g] | 31 | 8.9 |
| | RBZ 0.5 q4w [291] | 95 | 34 | 9.4 |

*BCVA* best-corrected visual acuity, *BL* baseline, *CI* confidence interval, *ETDRS* Early Treatment Diabetic Retinopathy Study, *FAS* full analysis set, *IAI* intravitreal aflibercept injection, *LOCF* last observation carried forward, *NR* not reported, *pt(s)* patient(s), *qxw* every *x* weeks, *RBZ* ranibizumab

* $p < 0.01$ vs. RBZ 0.5 q4w

[a] FAS with LOCF

[b] Data for the IAI 2 mg q4w, IAI 2 mg q8w and RBZ 0.5 mg q4w arms in these trials are derived from the US prescribing information [19] and/or a press release [33]; data for the IAI 0.5 mg q4w arms are derived from abstracts (VIEW 1 [34] and 2 [35]) and/or a press release [33]

[c] Primary endpoint

[d] Maintained = loss of <15 ETDRS letters compared with BL; improved = gain of ≥15 ETDRS letters compared with BL

[e] IAI was noninferior to RBZ, as the 95 % CI for the between-group difference (IAI − RBZ) (NR for IAI 0.5 q4w vs. RBZ; −2.4, 5.0 for IAI 2 q4w vs. RBZ; and −3.2, 4.4 for IAI 2 q8w vs. RBZ) lay entirely below (the noninferiority margin of) 10 %

[f] First three doses were administered at 1-month intervals

[g] IAI was noninferior to RBZ, as the 95 % CI for the between-group difference (IAI − RBZ) (NR for IAI 0.5 q4w vs. RBZ; −4.0, 3.3 for IAI 2 q4w vs. RBZ; and −2.9, 4.0 for IAI 2 q8w vs. RBZ) lay entirely below (the noninferiority margin of) 10 %

## 5 Tolerability

The following tolerability profile of intravitreal aflibercept is based on pooled findings from the pivotal phase III VIEW studies discussed in Sect. 4; these have been reported in the US prescribing information [19] and/or the US FDA's regulatory review [23, 38].

A total of 1,824 patients (911 and 913 in VIEW 1 and 2, respectively) were treated with aflibercept for 52 weeks, including 613 (304 and 309 in VIEW 1 and 2, respectively) who received 2 mg every month and 610 (303 and 307 in VIEW 1 and 2, respectively) who received 2 mg every second month [19, 31, 32].

### 5.1 Ocular Adverse Events

Of the 1,824 aflibercept recipients, 1,263 (69.2 %) reported at least one treatment-emergent ocular adverse event (in the study eye); 36 (2.0 %) reported at least one treatment-emergent serious ocular adverse event [38]. Among the 595 patients who received ranibizumab in the two VIEW studies, 433 (72.8 %) reported at least one treatment-emergent ocular adverse event; 19 (3.2 %) reported at least one treatment-emergent serious ocular adverse event [38].

The most common (incidence ≥5 %) treatment-emergent ocular adverse events occurring in aflibercept recipients were conjunctival haemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters and increased intraocular pressure (IOP). The incidences of these (and other frequently reported ocular) adverse events in aflibercept recipients did not differ appreciably from those in ranibizumab recipients [19] (Fig. 1).

Three (0.2 %) of the 1,824 aflibercept recipients developed endophthalmitis; all three patients received the 2 mg every month regimen in VIEW 1. In comparison, three (0.5 %) of the 595 ranibizumab recipients developed endophthalmitis; all three patients were participants in the VIEW 1 trial [38].

Fifty-one (2.8 %) of the 1,824 patients treated with aflibercept, as compared with 22 (3.7 %) of the 595 patients treated with ranibizumab, had an absolute IOP value of ≥35 mm Hg during the study. The corresponding proportions of patients who had a ≥10 mm Hg increase in IOP from baseline during the study were 2.0 % and 3.2 %, respectively [38]. Increased IOP, which was noted

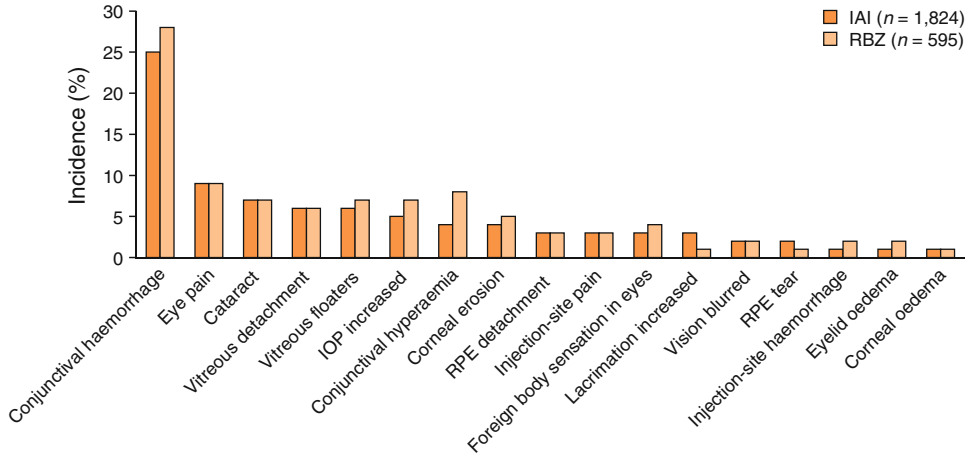


**Fig. 1** Comparative ocular tolerability of intravitreally administered aflibercept and ranibizumab in patients with neovascular age-related macular degeneration. The figure shows the pooled incidences of commonly occurring (incidence ≥1 %) treatment-emergent ocular adverse events in patients randomized to receive one of three aflibercept dosing regimens [0.5 mg every 4 weeks; 2 mg every 4 weeks; and 2 mg every 8 weeks (with the first three doses administered at 4-week intervals)] or the recommended regimen of ranibizumab (0.5 mg every 4 weeks) in two pivotal phase III studies (VIEW 1 and 2; see Table 1 for study design details) [19, 38]. *IAI* intravitreal aflibercept injection, *IOP* intraocular pressure, *RBZ* ranibizumab, *RPE* retinal pigment epithelium

within 1 h of intravitreal injection (of aflibercept), resolved in most patients before the next pre-dose measurement [19].

### 5.2 Non-Ocular Adverse Events

Of the 1,824 aflibercept recipients, 1,324 (72.6 %) reported at least one treatment-emergent non-ocular adverse event; 252 (13.8 %) reported at least one treatment-emergent serious non-ocular adverse event [38]. Among the 595 ranibizumab recipients, 415 (69.7 %) reported at least one treatment-emergent non-ocular adverse event; 83 (13.9 %) reported at least one treatment-emergent serious non-ocular adverse event [38].

Intravitreal administration of anti-VEGF agents to patients with neovascular AMD has been associated with the occurrence of arterial thromboembolic events (ATEs) [defined as non-fatal stroke, non-fatal myocardial infarction and vascular death (including deaths of unknown cause)] [19]. Across both trials, the incidence of ATEs was 1.8 % in patients treated with aflibercept (all dosage groups combined), as compared with 1.7 % in patients treated with ranibizumab [19, 38].

Nasal septal deviation, rhinorrhoea, epistaxis, nasal polyps, turbinate hypertrophy, nasal dryness and cysts were occasionally observed in a subset of VIEW 2 participants ($n = 160$; 40 per treatment group) who underwent a special ear, nose and throat examination. However, there were no reports of nasomucosal erosions (which have been seen in animal studies of aflibercept) [19, 23, 38].

## 6 Dosage and Administration

In the US, the recommended dosing schedule (per affected eye) for intravitreally injected aflibercept is 2 mg every month for the first 3 months followed by 2 mg every second month. Although aflibercept (2 mg per affected eye) may be administered every month from the outset of treatment, this regimen did not demonstrate greater efficacy compared with administration every second month after the three initial monthly doses [19] (see Sect. 4).

Aflibercept is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation [19].

Local prescribing information should be consulted for full details of dosage and administration instructions, as well as contraindications, warnings and precautions relating to the use of intravitreal aflibercept.

## 7 Current Status

Intravitreally administered aflibercept has been approved for the treatment of neovascular AMD in the US [19] and Australia [20].

This approval was based on the results of two well designed phase III studies (VIEW 1 and 2), which compared aflibercept with ranibizumab, the current gold standard for the treatment of neovascular AMD in the US. In both trials, which were of virtually identical design, the recommended regimen of aflibercept [2 mg every second

month (after three initial monthly doses)] was shown to be noninferior to the recommended regimen of ranibizumab (0.5 mg every month) in terms of the primary endpoint of maintaining vision after 1 year of treatment; similar results were seen when monthly dosing with aflibercept (0.5 or 2 mg) was compared with ranibizumab.

Furthermore, over a 96-week period, patients receiving aflibercept 2 mg every second month (after three initial monthly doses) during the first year followed by modified quarterly treatment during the second year had a similar visual acuity gain to those receiving ranibizumab every month during first year followed by modified quarterly treatment during the second year, but on average required five fewer injections.

Aflibercept was generally well tolerated in the VIEW studies; the ocular and non-ocular adverse event profile of the drug was similar to that of ranibizumab.

In the EU, the EMA's CHMP has adopted a positive opinion for the use of intravitreal aflibercept in the treatment of neovascular AMD [39].

**Disclosure** The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made by the author on the basis of scientific and editorial merit.

## References

1. Chappelow AV, Kaiser PK. Neovascular age-related macular degeneration: potential therapies. Drugs. 2008;68(8):1029–36.
2. La Cour M, Kiilgaard JF, Nissen MH. Age-related macular degeneration: epidemiology and optimal treatment. Drugs Aging. 2002;19(2):101–33.
3. de Jong PTVM. Age-related macular degeneration. N Engl J Med. 2006;355:1474–85.
4. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. Surv Ophthalmol. 1995;39(5):367–74.
5. Stewart MW. The expanding role of vascular endothelial growth factor inhibitors in ophthalmology. Mayo Clin Proc. 2012;87(1):77–88.
6. Waisbourd M, Loewenstein A, Goldstein M, et al. Targeting vascular endothelial growth factor: a promising strategy for treating age-related macular degeneration. Drugs Aging. 2007;24(8):643–62.
7. Takahashi H, Shibuya M. The vascular endothelial growth factor (VEGF)/VEGF receptor system and its role under physiological and pathological conditions. Clin Sci (Lond). 2005;109(3):227–41.
8. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003;9(6):669–76.
9. Vinores SA. Pegaptanib in the treatment of wet, age-related macular degeneration. Int J Nanomed. 2006;1(3):263–8.
10. Blick SKA, Keating GM, Wagstaff AJ. Ranibizumab. Drugs. 2007;67(8):1199–206.
11. Frampton JE. Ranibizumab: in diabetic macular oedema. Drugs. 2012;72(4):509–23.
12. The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;19(364):1897–908.
13. Kovach JL, Schwartz SG, Flynn HW Jr, et al. Anti-VEGF treatment strategies for wet AMD. J Ophthalmol. 2012;2012:786870. (Epub 2012 Feb 28).
14. Stewart MW, Grippon S, Kirkpatrick P. Aflibercept. Nat Rev Drug Discov. 2012;11(4):269–70.
15. Stewart MW. Aflibercept (VEGF Trap-eye): the newest anti-VEGF drug. Br J Ophthalmol. (Epub 2012 Mar 23).
16. Papadopoulous N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis. 2012;15(2):171–85.
17. Zhang F, Tang Z, Hou X, et al. VEGF-B is dispensible for blood vessel growth but critical for their survival, and VEGF-B targeting inhibits pathological angiogenesis. PNAS. 2009;106(15):6152–7.
18. Rakic J-M, Lambert V, Devy L, et al. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. Invest Ophthalmol Vis Sci. 2003;44:3186–93.
19. EYLEA™ (aflibercept) injection: US prescribing information. Tarrytown (NY); Regeneron Pharmaceuticals, Inc. http://www.regeneron.com/Eylea/eylea-fpi.pdf. Accessed 2 Apr 2012.
20. Regeneron Pharmaceuticals, Inc. Regeneron and Bayer announce approval of EYLEA™ (aflibercept) injection for the treatment of wet age-related macular degeneration in Australia [media release]. 2012 Mar 8. http://investor.regeneron.com. Accessed 2 Apr 2012.
21. Holash J, Davis S, Papadopoulos N, et al. VEGF-trap: a VEGF blocker with potent antitumor effects. PNAS. 2002;99(17):11393–8.
22. Konner JDJ. Use of soluble recombinant decoy receptor vascular endothelial growth factor trap (VEGF trap) to inhibit vascular endothelial growth factor activity. Clin Colorectal Cancer. 2004;4(Suppl. 2):S81–5.
23. Application number: 125387Orig1s000. Pharmacology review(s). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000PharmR.pdf. Accessed 4 Apr 2012.
24. Brown DM, Heier JS, Ciulla T, et al. Primary endpoint results of a phase II study of vascular endothelial growth factor trap-eye in wet age-related macular degeneration. Ophthalmology. 2011;118(6):1089–97.
25. Rudge JS, Holash J, Hylton D, et al. VEGF trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. PNAS. 2007;104(47):18363–70.
26. Bhisitkul RB. Vascular endothelial growth factor biology: clinical implications for ocular treatments. Br J Ophthalmol. 2006;90:1542–7.
27. Wiegand SJ, Zimmer E, Nork TM, et al. VEGF trap both prevents experimental choroidal neovascularization and causes regression of established lesions in non-human primates. Invest Ophthalmol Vis Sci. 2005; 46: E-abstract 1411-B180. http://abstracts.iovs.org/cgi/content/abstract/46/5/1411. Accessed 4 Apr 2012.
28. Saishin Y, Saishin Y, Takahashi K, et al. VEGF-trap (R1R2) suppresses choroidal neovascularization and VEGF-induced breakdown of the blood-retinal barrier. J Cell Physiol. 2003;195(2):241–8.
29. Nguyen QD, Shah SM, Browning DJ, et al. A phase I study of intravitreal vascular endothelial growth factor trap-eye in patients with neovascular age-related macular degeneration. Ophthalmology. 2009;116(11):2141-8.e1.
30. Application number: 125387Orig1s000. Clinical pharmacology and biopharmaceutics review(s). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000ClinPharmR.pdf. Accessed 4 Apr 2012.

31. Regeneron. Vascular endothelial growth factor (VEGF) trap-eye: investigation of efficacy and safety in wet age-related macular degeneration (AMD) (VIEW 1) [ClinicalTrials.gov identifier NCT00509795]. US National Institutes of Health, ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT00509795. Accessed 2 Apr 2012.
32. Bayer. Vascular endothelial growth factor (VEGF) trap-eye: investigation of efficacy and safety in wet age-related macular degeneration (AMD) (VIEW 2) [ClinicalTrials.gov identifier NCT00637377]. US National Institutes of Health, ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT00637377. Accessed 2 Apr 2012.
33. Regeneron Pharmaceuticals, Inc. Bayer and Regeneron report positive top-line results of two phase 3 studies with VEGF Trap-EYE in wet age-related macular degeneration [media release]. http://investor.regeneron.com. Accessed 22 Nov 2010.
34. Nguyen QD, Heier J, Brown D, et al. Randomized, double-masked, active-controlled phase 3 trial of the efficacy and safety of intravitreal VEGF-Trap-Eye in wet AMD: one-year results of the VIEW-1 study [abstract no. 3073]. 2011 Annual Meeting of the Association for Research in Vision and Ophthalmology; 2011 May 1-5; Fort Lauderdale (FL).
35. Schmidt-Erfurth U, Chong V, Kirchhof B, et al. Primary results of an international phase III study using intravitreal VEGF Trap-Eye compared to ranibizumab in patients with wet AMD (VIEW 2) [abstract no. 1650]. 2011 Annual Meeting of the Association for Research in Vision and Ophthalmology; 2011 May 1–5; Fort Lauderdale (FL).
36. Heier JS, Boyer D, Nguyen QD, et al. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. Ophthalmology. 2011;118(6):1098–106.
37. Regeneron Pharmaceuticals, Inc. Two year results of phase 3 studies with EYLEA™ (aflibercept) injection in wet AMD show sustained improvement in visual acuity [media release]. http://investor.regeneron.com. Accessed 5 Dec 2011.
38. Application number: 125387Orig1s000. Medical review(s). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000MedR.pdf. Accessed 4 Apr 2012.
39. European Medicines Agency, Committee for Medicinal Products for Human Use. Summary of opinion (initial authorization): Eylea (aflibercept). http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002392/WC500132884.pdf. Accessed 28 Sep 2012.