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REVIEW ARTICLE

Comparative Safety and Tolerability of Anti-VEGF Therapy in Age-Related Macular Degeneration

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Abstract Neovascular age-related macular degeneration (NVAMD) is one of the leading causes of blindness. Over the last decade, the treatment of NVAMD has been revolutionized by the development of intravitreal anti-vascular endothelial growth factor (VEGF) therapies. Several anti-VEGF medications are used for the treatment of NVAMD. The safety and tolerability of these medications deserve review given the high prevalence of NVAMD and the significant utilization of these medications. Numerous large randomized clinical trials have not shown any definitive differential safety relative to ocular or systemic safety of these medications. Intravitreal anti-VEGF therapy does appear to impact systemic VEGF levels, but the implications of these changes remain unclear. One unique safety concern relates drug compounding and the potential risks of contamination, specifically for bevacizumab. Continued surveillance for systemic safety concerns, particularly for rare events, is merited. Overall, these medications are well tolerated and effective in the treatment of NVAMD.

Key Points

Anti-vascular endothelial growth factor (VEGF) therapy has revolutionized the care of neovascular age-related macular degeneration (NVAMD), dramatically improving the visual outcomes.

Anti-VEGF agents are generally well-tolerated, and the safety risks appear to be reasonably small relative to the benefits of therapy.

Ocular safety concerns, such as endophthalmitis or retinal detachment, are likely primarily related to the injection procedure rather than the specific medication used.

While none of the clinical trials were adequately powered to directly assess safety, a review of numerous randomized trials suggests that systemic safety between the three major drugs appear fairly similar.

1 Introduction

Age-related macular degeneration (AMD) is a progressive disease of the central retina and is the leading cause of irreversible central vision loss and legal blindness in individuals aged 65 years or older in Western countries [1–4]. AMD is classified into two well-defined but frequently overlapping clinical forms. Approximately 85 % of those affected by the disease manifest the nonexudative form, which is characterized by abnormalities of the retinal pigment epithelium (RPE) and drusen [5]. While investigations are ongoing to

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evaluate treatment of this form, there remains no approved treatment for the nonexudative form of AMD. However, the use of a vitamin formulation has demonstrated slowed progression to advanced forms of AMD in certain groups [6]. The exudative (or neovascular) form is defined by the presence of choroidal neovascularization (CNV) with associated fluid exudation or bleeding. Untreated, severe vision loss most frequently occurs secondary to subretinal fibrosis and scarring. While CNV accounts for only 15 % of all AMD patients, it accounts for approximately 80 % of severe central vision loss in AMD [7].

The exudative form of AMD (neovascular AMD [NVAMD]) has been characterized by an upregulation of angiogenic factors, including vascular endothelial growth factor (VEGF), demonstrating a reproducible role in this pathogenesis [8–10]. As VEGF has been implicated in the progression of the exudative form, blockade of this angiogenic factor is a natural target. In 2004, the treatment of NVAMD dramatically changed with the initiation of anti-VEGF therapy. Contrary to its predecessor treatments, including laser photocoagulation, photodynamic therapy, macular translocation, and submacular surgery, this treatment demonstrated not only stability of vision but also an improvement in visual acuity in certain patients [11]. The first case of an 'off label' intravitreal anti-VEGF agent (bevacizumab) being used to treat a patient with NVAMD and to demonstrate improvement in retinal thickness by optical coherence tomography (OCT) that was sustained for 4 weeks was reported in 2005 [12]. The first randomized clinical studies on anti-VEGF agents (pegaptanib and ranibizumab) to demonstrate efficacy initiated mandated monthly scheduled injections in study patients [13–17]. Not surprisingly, the high frequency of injections in this chronic and progressive condition raised concerns of ocular and systemic safety of this relatively new class of pharmacotherapy [1].

In this report, we provide a brief overview of the clinical efficacy of anti-VEGF therapy and review the systemic and ocular adverse events associated with anti-VEGF agents and draw comparisons between the drugs.

2 Methods

A systematic search of PubMed and Cochrane library databases was performed to comprehensively gather and analyze the various applicable studies in order to compare and contrast the safety profiles of different intravitreal anti-VEGF therapies. A start date of January 2003 and an end date of December 2014 was established to collect all pertinent information from clinical trials, metanalysis, reviews, observational studies, and case reports. The key terms used in the search included the following: age-related macular degeneration, choroidal neovascularization (CNV), anti-vascular endothelial growth factor therapy, pegaptanib, bevacizumab, ranibizumab, aflibercept, systemic adverse events, ocular adverse events, and anti-VEGF compounding. Secondary searches included articles cited in reference lists identified by the primary search. Only studies published in English were included.

3 Results

3.1 Anti-Vascular Endothelial Growth Factor (VEGF) Therapy and Clinical Efficacy

Four anti-VEGF agents are currently used in clinical practice for the intravitreal treatment of NVAMD. Table 1 summarizes the visual gains of the control groups, pegaptanib, bevacizumab, ranibizumab, and aflibercept arranged by clinical study.

3.1.1 Pegaptanib

Pegaptanib (Macugen®; Eyetech Inc., FL/Pfizer Inc., NY/Bausch & Lomb, NY/Valeant Pharmaceuticals International, NJ, USA) was the first therapy approved by the US FDA in 2004 for the treatment of NVAMD. Pegaptanib is an RNA aptamer that specifically inhibits the VEGF-A 165 isoform. This is in contrast to the other anti-VEGF agents, which inhibit all isoforms of VEGF-A.

The VISION (VEGF Inhibition Study in Ocular Neovascularization) trial demonstrated the superiority of pegaptanib relative to sham injections when assessing visual acuity [13, 18]. However, this anti-VEGF treatment has largely been supplanted by bevacizumab, ranibizumab, and aflibercept, which demonstrate pan VEGF-A inhibition and enhanced clinical efficacy. Given its limited use in clinical practice, further discussion focuses on the following three frequently used anti-VEGF agents: bevacizumab, ranibizumab, and aflibercept.

3.1.2 Bevacizumab

Bevacizumab (Avastin; Genentech/Roche, South San Francisco, CA, USA) is a murine humanized monoclonal antibody (149 kDa) that inhibits all isoforms of VEGF-A. In 2004, it was approved for the treatment of metastatic colorectal cancer. Systemic adverse events associated with intravenous administration for oncology applications include thromboembolic events (myocardial infarction [MI], cerebrovascular accident [CVA], central nervous system [CNS] haemorrhage), hemoptysis, gastrointestinal perforation, and wound healing complications [19]. In 2004, the SANA (Systemic Avastin for Neovascular AMD) trial was

Table 1 Major randomized control trials evaluating anti-vascular endothelial growth factor therapy for the treatment of exudative age-related macular degeneration: characteristics and visual outcomes

Clinical trial (year published) and no. in each arm	Treatment group	Dose/injection/ treatment regimen	Mean no. of study injections	Follow-up (years)	Mean change in vision (letters)	Completion rate
VISION (2004) [13]						90
298	–	Sham q6 weeks	0	1	−14.8	–
295	Pegaptanib	0.3 mg q6 weeks	8.4	1	−7.5	–
301	Pegaptanib	1.0 mg q6 weeks	8.5	1	−6.5	–
296	Pegaptanib	3.0 mg q6 weeks	8.4	1	−10.0	–
MARINA (2006) [17]						
238	–	Sham monthly	0	2	−14.9	79.8
238	Ranibizumab	0.3 mg monthly	24	2	+5.4	88.2
240	Ranibizumab	0.5 mg monthly	24	2	+6.6	89.6
ANCHOR (2009) [14]						
143	Verteporfin	Sham monthly injections + PDT	–	2	−9.8	76.9
140	Ranibizumab	0.3 mg monthly + sham PDT	21.5	2	+8.1	83.6
140	Ranibizumab	0.5 mg monthly + sham PDT	21.3	2	+10.7	82.9
PIER (2010) [29]						
63	–	Sham monthly × 3, then quarterly (crossover in year 2 to monthly 0.5 mg ranibizumab)	4.1	2	−21.4	73.0
60	Ranibizumab	0.3 mg monthly × 3, then quarterly	10.6	2	−2.2	88.3
61	Ranibizumab	0.5 mg monthly × 33, then quarterly	10.5	2	−2.3	88.5
ABC (2010) [22]						96
66	Standard Care	PDT (for predominantly classic AMD) ($N = 16$) or pegaptanib (for minimally classic or occult AMD) ($N = 38$) or sham treatment ($N = 12$)	PDT : 3.2 treatments; Pegaptanib: 8.9	1	−9.4	–
65	Bevacizumab	1.25 mg q6 weeks × 3, then q6 weeks PRN	7.1	1	+7.0	–
EXCITE (2011) [31]						
120	Ranibizumab	0.3 mg monthly × 3, then quarterly	5.7	1	+4.0	88.3
118	Ranibizumab	0.5 mg monthly × 3, then quarterly	5.5	1	+2.8	80.5
115	Ranibizumab	0.3 mg monthly	11.4	1	+8.0	89.6
CATT (2012) [24]						
301	Ranibizumab	0.5 mg monthly	22.4	2	+8.8	88.7
	Ranibizumab	0.5 mg monthly (year 1); 0.5 mg PRN (year 2)	17.0	2	+6.8	91.8
298	Ranibizumab	0.5 mg PRN	12.6	2	+6.7	91.7
286	Bevacizumab	1.25 mg monthly	23.4	2	+7.8	91.9
	Bevacizumab	1.25 mg monthly (year 1); 1.25 mg PRN (year 2)	17.8	2	+4.6	91.7
300	Bevacizumab	1.25 mg PRN	14.1	2	+5.0	91.3

Table 1 continued

Clinical trial (year published) and no. in each arm	Treatment group	Dose/injection/ treatment regimen	Mean no. of study injections	Follow-up (years)	Mean change in vision (letters)	Completion rate
MANTA (2013) [27]						
163	Ranibizumab	0.5 mg monthly × 3, then PRN	5.8	1	+4.1	–
154	Bevacizumab	1.25 mg monthly × 3, then PRN	6.1	1	+4.9	–
IVAN (2013) [23]						87
157	Ranibizumab	0.5 mg monthly	18	2	+6.0	–
155	Ranibizumab	0.5 mg monthly PRN				
149	Bevacizumab	1.25 mg monthly	19	2	+5.0	–
145	Bevacizumab	1.25 mg monthly PRN				
GEFAL (2013) [26]						
239	Ranibizumab	0.5 mg monthly × 3, then PRN	5.8	1	+2.9	–
246	Bevacizumab	1.25 mg monthly × 3, then PRN	6.1	1	+4.8	–
VIEW 1/2 (2014) [37]						
595	Ranibizumab	0.5 mg monthly	16.5	2	+7.9	85.2
613	Aflibercept	2.0 mg monthly	16.0	2	+7.6	85.7
601	Aflibercept	0.5 mg monthly	16.2	2	+6.6	81.6
610	Aflibercept	2.0 mg monthly × 3, then q8 weeks	11.2	2	+7.6	83.3
HARBOR (2014) [71]						
275	Ranibizumab	0.5 mg monthly	21.4	2	+9.1	83.6
275	Ranibizumab	0.5 mg monthly × 3, then PRN	13.3	2	+7.9	86.2
274	Ranibizumab	2.0 mg monthly	21.6	2	+8.0	87.2
273	Ranibizumab	2.0 mg monthly × 3, then PRN	11.2	2	+7.6	86.8
LUCAS (2015) [45]						
221	Ranibizumab	0.5 mg monthly until inactive then extended × 2 weeks up to a maximum of 12 weeks	8.0	1	+8.2	84.6
220	Bevacizumab	1.25 mg monthly until inactive, then extended × 2 weeks up to a maximum of 12 weeks	8.9	1	+7.9	83.6

AMD age-related macular degeneration, N number, *PDT* photodynamic therapy, *PRN* pro re nata (as needed), *q* every, – indicates not reported or not identified

initiated, with 18 patients receiving two intravenous infusions of bevacizumab 5 mg/kg at 2-week intervals. Systemic side effects included mildly elevated systolic blood pressure that was adequately controlled with antihypertensive medications. Notably, a 14-letter improvement in mean visual acuity at 24 weeks was observed [20, 21]. The intravitreal dose of bevacizumab is 200–400 times less than the intravenous dose [12]. Since the introduction of intravitreal bevacizumab therapy in 2005, this medication has been frequently used 'off label' for the treatment of NVAMD.

In 2010, the randomized double-masked ABC (Study of the Efficacy and Safety of Avastin (Bevacizumab) Intravitreal Injections Compared to Standard Therapy in Subjects with Choroidal Neovascularization Secondary to Age-Related Macular Degeneration) trial results were published [22]. This study compared intravitreal bevacizumab 1.25 mg (given as three loading doses every 6 weeks, followed by additional injections given every 6 weeks as needed based on OCT parameters) against verteporfin photodynamic therapy (PDT) or pegaptanib (the previously recognized standards of care). At the conclusion of the 1-year study, the mean change in vision was +7.0 letters in the bevacizumab group and −9.4 letters in the other group, demonstrating for the first time the clear efficacy of bevacizumab for the treatment of NVAMD.

Given the initial lack of randomized clinical trials, the potential systemic and ocular adverse events extrapolated from intravenous data remained concerning. Recent comparison trials between intravitreal bevacizumab and ranibizumab have compared both systemic and ocular adverse events between the drugs, with no appreciable difference attributed to the anti-VEGF therapy (discussed below) [23–28].

3.1.3 Ranibizumab

Ranibizumab (Lucentis; Genentech/Roche, South San Francisco, CA, USA) is a humanized monoclonal antibody consisting of the Fab fragment (48 kD), which suppresses all VEGF-A isoforms. The differentiating feature between ranibizumab and bevacizumab is the smaller size and absence of the Fc receptor.

The phase III randomized double-masked studies were the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration) study [14] and the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration) study [16]. ANCHOR was randomized 1:1:1 to receive either monthly injections of ranibizumab 0.3 mg or 0.5 mg (plus verteporfin sham PDT) or monthly sham injections plus active verteporfin PDT as needed every 3 months. The mean change in visual acuity was +10.7 letters in the ranibizumab 0.5 mg group and −9.8 letters in the active PDT group, demonstrating similar efficacy to that in the ABC study [14]. Similarly, the MARINA study at 24 months demonstrated a mean of +7.2 letters in the ranibizumab 0.5 mg group and −10.4 letters in the sham group [16].

Several additional studies evaluating ranibizumab administered as needed (PrONTO [Prospective OCT Imaging of Patients with Neovascular AMD Treated with intraOcular Ranibizumab] study) or with increased timing between injections (PIER [A Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal CNV with or without Classic CNV Secondary to AMD] and EXCITE [Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular AMD] have also been studied and demonstrate uniformly positive improvements of ranibizumab over the control arm. However, PIER [29, 30] and EXCITE [31] demonstrated better results in monthly injections relative to quarterly injections. PrONTO demonstrated that OCT-guided variable-dosing of intravitreal ranibizumab yielded visual acuity outcomes that were comparable to mandated monthly injections, albeit with fewer intravitreal injections [32, 33].

3.1.4 Aflibercept

Aflibercept (Eylea, Regeneron, Tarrytown, NY, USA/Bayer, Basel, Switzerland) or VEGF Trap-eye is the newest member of the anti-VEGF class of NVAMD agents.

Aflibercept is a fully human, recombinant, soluble protein (110 kD) consisting of VEGF receptor sequences (VEGFR1 and VEGFR2) fused to an immunoglobulin (Ig)-G backbone. Its pharmacologic properties and efficacy have been previously explained in detail [34]. Briefly, while it binds all VEGF-A isoforms (like bevacizumab and ranibizumab, albeit with stronger affinity), it additionally binds VEGFR1 ligands, VEGF-B, and placental growth factor (PlGF) [35].

The VIEW-1 and -2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) studies were similarly designed prospective double-masked randomized clinical trials. Patients with exudative AMD were randomized 1:1:1:1 to 0.5 mg aflibercept monthly (0.5q4), 2 mg aflibercept monthly (2q4), 2 mg aflibercept every 2 months (following 3 monthly loading doses; 2q8), or 0.5 mg ranibizumab monthly (Rq4) during the first year of study. The mean visual acuity gains were similar across all treatment groups from baseline to 2 years, +6.6, +7.6, +7.6, and +7.9 letters for the 0.5q4, 2q4, 2q8, and Rq4

groups, respectively. This visual gain was similar to data for bevacizumab and ranibizumab at 2 years, but offers the potential for fewer injections in the 2-month dosing treatment strategy [36, 37].

3.2 Systemic VEGF Levels After Intravitreal Anti-VEGF Therapy

Intravitreal administration of 1.25 mg bevacizumab has been demonstrated to significantly reduce systemic VEGF levels after intravitreal injection [25, 38–40]. At 28 days after the initial injection, the median VEGF levels were 42 % lower than baseline ($p = 0.0002$) in eyes receiving intravitreal bevacizumab compared with 0.7 % lower in the ranibizumab group [39]. However, in the IVAN (Inhibit VEGF in Age-related Choroidal Neovascularization) study, both bevacizumab and ranibizumab resulted in significant reductions in serum VEGF levels from baseline [25]. The reduction was more significant in the bevacizumab group. Additionally, continuous therapy with anti-VEGF therapy resulted in more significant systemic VEGF reduction than discontinuous [23].

Yoshida et al. [41] evaluated plasma VEGF levels after administration of aflibercept and ranibizumab. They noted significant reductions in plasma VEGF levels after aflibercept administration that persisted up to 1 month. However, there was no change in the VEGF plasma levels in the ranibizumab group.

Various theories exist for the differential in systemic VEGF suppression. The presence of the Fc fragment of the antibody, which interacts with a neonatal Fc receptor found on endothelial cells, may impact the amount of VEGF suppression. This interaction between the receptor and Fc component of the antibody may result in translocation of the antibody across the blood–retina barrier and into systemic circulation [40]. Additionally, immunoglobulins containing an Fc region demonstrate a longer systemic half-life relative to proteins lacking this domain. This observation is thought to be secondary to Fc-receptor interaction, which protects the immunoglobulin from systemic catabolism [38].

3.3 Systemic Adverse Events

Given the known effects on plasma VEGF levels with intravitreal anti-VEGF therapy and the known small but significant rates of thromboembolic events (MI, CVA, CNS hemorrhage), gastrointestinal perforation, and wound healing complications after systemic administration of bevacizumab in oncology patients, there is a logical concern for the potential for systemic effects related to intravitreal administration [19]. However, recent comparative randomized trials between bevacizumab and ranibizumab as well as aflibercept and ranibizumab have not demonstrated a meaningful difference in the rates of major systemic adverse events [23, 24, 26–28, 36]

Ranibizumab has been well studied in several phase III randomized controlled trials (MARINA [16], ANCHOR [14], PIER [29], EXCITE [31], SUSTAIN [Study of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration] [42], SAILOR [Safety Assessment of Intravitreal Lucentis for AMD] [43]) with over 1500 patients cumulatively. In the MARINA study, rates of systemic arterial thromboembolic events were reportedly as high as 4.6 % in the ranibizumab-treated arm compared with 3.8 % in the sham-treated patients [16]. The PIER group demonstrated no patients with thromboembolic events in both the ranibizumab and the control group, demonstrating variability in the rates of adverse events but without difference between the treatment and control arms within studies [29]. While the SAILOR study demonstrated a higher rate of cerebrovascular stroke with ranibizumab 0.5 mg (1.2 %) than with ranibizumab 0.3 mg (0.7 %), this trend was not statistically significant [43]. Given these findings, Schmidt-Erfurth [44] concluded in a review of the literature that ranibizumab was well tolerated and not associated with any systemic adverse events with up to 2 years of treatment.

Given the off-label use of bevacizumab, data sets are less robust compared with those for ranibizumab. Nonetheless, comparative trials evaluating bevacizumab and ranibizumab efficacy, including CATT [28] (Comparison of Age-Related Macular Degeneration Treatments Trials), IVAN [25], GEFAL (Groupe d'Evaluation Français Avastin Versus Lucentis) [26], MANTA (Avastin Versus Lucentis in Age-Related Macular Degeneration) [27], and LUCAS (Lucentis Compared to Avastin Study) [45] have been undertaken and published. The first of these trials, CATT, was designed to directly compare the efficacy of bevacizumab versus ranibizumab, administered monthly or as needed for NVAMD. This study demonstrated equivalent visual acuity gains in the monthly and as-needed treatment groups between bevacizumab and ranibizumab. Thromboembolic events (MI and CVA) and rates of death were similar between all study arms ($p > 0.20$). However, a statistically significant higher portion of patients with one or more systemic serious adverse events (mostly hospitalizations) was observed between bevacizumab (39.9 %) and ranibizumab (31.7 %). Given that many of these conditions lacked an association with VEGF inhibition, the authors speculated this finding was not particular to the drugs but some additional unforeseen influence [28]. The IVAN, GEFAL, and MANTA studies similarly demonstrated no difference between rates of thromboembolic events between the ranibizumab and bevacizumab arms, further

substantiating the results of CATT [23, 26, 27]. Conversely, LUCAS demonstrated higher rates of arteriothrombotic events in the ranibizumab group than in the bevacizumab group ($p = 0.05$) and higher rates of nonfatal MI in the ranibizumab group ($p = 0.01$). Of note, the number of patients with a history of MI was higher in the ranibizumab group at baseline ($p = 0.021$), which may explain this difference [45]. Similar to the preceding studies, this study was not powered to detect meaningful differences in systemic adverse events. Detecting differences between rare systemic side effects, therefore, would necessitate a larger number of patients in future studies or rigorous meta-analyses to detect small differences in adverse events.

Other approaches have also been utilized to assess systemic safety. Curtis et al. [46] retrospectively evaluated 146,942 Medicare beneficiaries receiving treatment for NVAMD. The authors concluded that patients receiving bevacizumab or ranibizumab were not associated with an increased risk of mortality, MI, bleeding, or CVA when compared with patients receiving PDT. A Cochrane meta-analysis evaluating 3665 participants from non-industry-sponsored clinical trials similarly addressed the safety concerns between bevacizumab and ranibizumab. The estimated relative risk for all serious systemic adverse events was 1.08 (95 % confidence interval [CI] 0.78–1.31, $p = 0.59$). Based on the event rates, this translates to total adverse event percentages of 22.2 % for ranibizumab and 24 % for bevacizumab (95 % CI 20–29.1). Notably, the risk of gastrointestinal disorders was higher in the bevacizumab arms (relative risk [RR] 1.82, 95 % CI 1.04–3.19, $p = 0.04$) [47]. Given these results, the authors concluded that if a difference exists in systemic adverse events between the drugs, it is likely to be quite small.

Aflibercept is a newer drug on the market, only have received FDA approval for the treatment of NVAMD in 2011. Much of the safety analysis has been contributed from the parallel VIEW-1 and VIEW-2 studies, which evaluated different aflibercept doses and variable dosing time points (monthly or every other month) for aflibercept compared with monthly ranibizumab. The authors noted no significant difference in rates of all serious adverse events, MI, or stroke between the study arms [37].

Taken together, these data demonstrate no conclusive differences in rates of thromboembolic events or all-cause mortality between bevacizumab, ranibizumab, and aflibercept. As the utilization of these drugs continues to expand, this is an important area of continued surveillance. Table 2 summarizes serious systemic adverse events in some of the major randomized clinical trials in the literature, including the treatment and control arms.

3.4 Ocular Adverse Events

With intravitreal injections of anti-VEGF agents, serious ocular complications, including, but not limited to, endophthalmitis, intraocular inflammation, retinal detachment, elevated intraocular pressure (IOP), and subretinal and vitreous hemorrhage have been reported [48]. Many of these adverse events are likely more related to the act of having an intravitreal injection than related to drug class.

Endophthalmitis is one of the most serious of these risks, with the incidence ranging from 0.019 to 1.6 % [49, 50]. The comparative trials of bevacizumab and ranibizumab, including CATT [28], IVAN [25], GEFAL [26], MANTA [27], and LUCAS [45], have not demonstrated a difference in the rates of endophthalmitis between study arms. A large retrospective studying evaluating 12,585 bevacizumab injections and 14,320 ranibizumab injections demonstrated endophthalmitis rates of 0.02 % for both drugs (three eyes each) [51]. The rates of endophthalmitis after aflibercept in the VIEW-1 and -2 studies (0.2–0.8 %) are similarly within the reported range for bevacizumab and ranibizumab, suggesting no difference in rates of endophthalmitis based on drug used [37].

Studies have suggested that the organisms cultured from these cases of endophthalmitis demonstrate streptococcus species at a rate more frequent than after intraocular surgery [49]. As many of the species isolated were consistent with salivary flora, this suggested a contamination of the injection field by droplet spread or aerosolization from the patient's, tech's, or physician's mouth. While the procedure for intravitreal injection varies widely from practice to practice, precautions, including 5 % povidone iodine in the conjunctival fornix, consideration for use of a sterile lid speculum to avoid needle contact with the lashes, and the use of a mask or avoidance of talking may be reasonable safety precautions to minimize technique-related cases of endophthalmitis [48].

Intraocular inflammation has been reported to occur at a rate of 0.09–2.9 % [52]. The severity of this can range from mild intraocular inflammation to the rare cases of 'pseudoendophthalmitis' or sterile endophthalmitis. This rate has been reported to be between 0.09 and 0.4 % for bevacizumab [1, 52]. 4 and 2.9 % for ranibizumab [52], and 0.05 % for aflibercept based on reporting by Regeneron Pharmaceuticals. One differentiating feature of sterile endophthalmitis may include onset within 1 day of injection compared with true endophthalmitis occurring on average 2.5 days after injection [53]. Nonetheless, given multiple overlapping features, including pain, fibrin, and hypopyon, these patients should be evaluated and most often treated like true endophthalmitis with vitreous sampling and injection of intravitreal antibiotics [54].

Table 2 Major randomized control trials evaluating anti-vascular endothelial growth factor therapy for the treatment of exudative age-related macular degeneration: major adverse systemic events

Clinical trial (year published) and no. in each arm	Treatment group	Dose/injection/ treatment regimen	BP elevation	MI	Stroke	All cause death	All major adverse events
VISION (2004) [13]							
298	–	Sham q6 weeks	15 (5.1)	9 (3.0)[a]		6 (2.0)	45 (15.1)
295	PEG	0.3 mg q6 weeks	26 (8.8)	30 (3.4)[a,b]		19 (2.1)[b]	55 (18.6)
301	PEG	1.0 mg q6 weeks	29 (9.7)				50 (16.6)
296	PEG	3.0 mg q6 weeks	22 (7.4)				64 (21.6)
MARINA (2006) [17]							
238	–	Sham monthly	38 (16.0)	4 (1.7)	2 (0.8)	6 (2.5)	63 (26.5)
238	RAN	0.3 mg monthly	41 (17.2)	6 (2.5)	3 (1.3)	5 (2.1)	77 (32.4)
240	RAN	0.5 mg monthly	39 (16.3)	3 (1.3)	6 (2.5)	6 (2.5)	75 (31.4)
ANCHOR (2009) [14]							
143	VER	Sham monthly injections + PDT	23 (16.1)	2 (1.4)	2 (1.4)	5 (3.5)	39 (27.3)
140	RAN	0.3 mg monthly + Sham PDT	13 (9.3)	1 (0.7)	3 (2.1)	5 (3.6)	34 (24.3)
140	RAN	0.5 mg monthly + Sham PDT	17 (12.1)	5 (3.6)	0	3 (2.1)	38 (27.1)
PIER (2010) [29]							
63	–	Sham monthly × 3, then quarterly (crossover in year 2 to monthly 0.5 mg RAN)	7 (11.1) sham	1 (1.6) sham	1 (1.6) RAN	1 (1.6) sham 1 (1.6) RAN	9 (14.3) sham 2 (3.2) RAN
60	RAN	0.3 mg monthly × 3, then quarterly	6 (10.0)	0	0	2 (3.3)	8 (13.3)
61	RAN	0.5 mg monthly × 3, then quarterly	13 (21.3)	0	0	0	13 (21.3)
ABC (2010) [22]							
66	SC	PDT (for predominantly classic AMD) ($N = 16$) or PEG (for minimally classic or occult AMD) ($N = 38$) or sham treatment ($N = 12$)	0	0	0	0	7 (10.6)
65	BEV	1.25 mg q6 weeks × 3, then q6 weeks PRN	0	1 (1.5)	0	1 (1.5)	3 (4.6)
EXCITE (2011) [31]							
120	RAN	0.3 mg monthly × 3, then quarterly	10 (8.3)	1 (0.8)	0	0	15 (12.5)
118	RAN	0.5 mg monthly × 3, the quarterly	6 (5.1)	0	0	2 (1.7)	23 (19.5)
115	RAN	0.3 mg monthly	8 (7.0)	1 (0.9)	1 (0.9)	1 (0.9)	20 (17.4)
CATT (2012) [24]							
301	RAN	0.5 mg monthly	3 (0.5)[b]	9 (1.5)[b]	8 (1.3)[b]	32 (5.3)[b]	190 (31.7)[b]
	RAN	0.5 mg monthly (year 1); 0.5 mg PRN (year 2)					
298	RAN	0.5 mg PRN					
286	BEV	1.25 mg monthly	4 (0.7)[b]	7 (1.2)[b]	8 (1.3)[b]	36 (6.1)[b]	234 (39.9)[b]
	BEV	1.25 mg monthly (year 1); 1.25 mg PRN (year 2)					
300	BEV	1.25 mg PRN					

Table 2 continued

Clinical trial (year published) and no. in each arm	Treatment group	Dose/injection/ treatment regimen	BP elevation	MI	Stroke	All cause death	All major adverse events
MANTA (2013) [27]							
163	RAN	0.5 mg monthly × 3, then PRN	–	2 (1.2)	1 (0.6)	2 (1.2)	15 (9.2)
154	BEV	1.25 mg monthly × 3, then PRN	–	3 (1.9)	1 (0.6)	3 (1.9)	19 (12.3)
IVAN (2013) [23]							
157	RAN	0.5 mg monthly	–	4 (1.3)[b]	6 (1.9)[b]	15 (4.8)[b]	81 (26.0)[b]
155	RAN	0.5 mg monthly PRN					
149	BEV	1.25 mg monthly	–	5 (1.7)[b]	3 (1.0)[b]	15 (5.1)[b]	80 (27.2)[b]
145	BEV	1.25 mg monthly PRN					
GEFAL (2013) [26]							
239	RAN	0.5 mg monthly × 3, then PRN	2 (0.8)	1 (0.4)	0	3 (1.3)	24 (10.0)
246	BEV	1.25 mg monthly × 3, then PRN	1 (0.4)	1 (0.4)	0	2 (0.8)	30 (12.2)
VIEW 1/2 (2014) [37]							
595	RAN	0.5 mg monthly	–	12 (2.0)	5 (0.8)	16 (2.7)	83 (13.9)
613	AFL	2.0 mg monthly	–	6 (1.0)	5 (0.8)	13 (2.1)	76 (12.4)
601	AFL	0.5 mg monthly	–	12 (2.0)	3 (0.5)	19 (3.2)	87 (14.5)
610	AFL	2.0 mg monthly × 3, then q8 weeks	–	7 (1.1)	5 (0.8)	20 (3.3)	89 (14.6)
HARBOR (2014) [71]							
275	RAN	0.5 mg monthly	0	7 (2.5)	2 (0.7)	13 (4.7)	45 (16.4)
275	RAN	0.5 mg monthly × 3, then PRN	1 (0.4)	5 (1.8)	1 (0.4)	10 (3.6)	41 (14.9)
274	RAN	2.0 mg monthly	1 (0.4)	8 (2.9)	2 (0.7)	10 (3.6)	43 (15.7)
273	RAN	2.0 mg monthly × 3, then PRN	3 (1.0)	7 (2.6)	3 (1.0)	11 (4.0)	40 (14.7)
LUCAS (2015) [45]							
221	RAN	0.5 mg monthly until inactive, then extended × 2 weeks up to a maximum of 12 weeks	0 (0.0)	6 (2.7)	3 (1.4)	7 (3.2)	65 (29.4)
220	BEV	1.25 mg monthly until inactive, then extended × 2 weeks up to a maximum of 12 weeks	2 (0.9)	0 (0.0)	2 (0.9)	4 (1.8)	41 (18.6)

Data are presented as *N* (%) unless otherwise indicated

AFL aflibercept, *AMD* age-related macular degeneration, *BEV* bevacizumab, *BP* blood pressure, *MI* myocardial infarction, *PDT* photodynamic therapy, *PEG* pegaptanib, *PRN* pro re nata (as needed), *q* every, *RAN* ranibizumab, *SC* standard care, *VER* verteporfin, – indicates not reported or not identified

[a] Thromboembolic events including stroke and MI were reported jointly

[b] Events for drug reported jointly

Rhegmatogenous retinal detachment after anti-VEGF agents is a rare complication occurring at a rate between 0 and 0.67 % [52, 55]. Rates of retinal detachment are similar between anti-VEGF agents [52]. The proposed etiology for detachment or retinal tear involves induction of vitreous traction or potentially posterior needle penetration through the retina [55].

The most commonly reported hemorrhage after anti-VEGF therapy is subconjunctival hemorrhage occurring in nearly 10 % of all injections, irrespective of medication used [56]. These subconjunctival hemorrhages are more of cosmetic than any visual concern. Cases of subretinal hemorrhage [57] and suprachoroidal hemorrhage [58] are limited mostly to case reports and remain rare complications after intravitreal injection. While a higher frequency of subconjunctival hemorrhage has been associated with patients taking aspirin, there is no indication to stop anticoagulation for this procedure [56].

Acute but transient elevations in IOP are a common finding after intravitreal anti-VEGF therapy. The IOP rise is transient, lasting a maximum of a few hours [59, 60]. There does not appear to be a difference between anti-VEGF therapies [52]. Although a transient IOP spike always occurs immediately following injection, reports are emerging of more sustained IOP elevation. Multiple factors are believed to potentially play a role, including trabecular meshwork injury or trabeculitis, larger injection volumes, smaller needle, and serial injections potentially resulting in impaired outflow from protein aggregates or silicone droplets [61–63]. Additionally, patients with comorbid glaucoma have demonstrated higher rates of IOP elevations after injection relative to controls [64]. This transient IOP spike may be mitigated by the administration of antihypertensive drops prior to the injection. A combination brimonidine/timolol drop administered twice a day before and on the day of injection was shown to significantly reduce the presence and duration of the IOP spike after ranibizumab administration [65].

Finally, while not an immediate ocular adverse event associated with anti-VEGF therapy, geographic atrophy (GA) has been reported in both IVAN and CATT to occur at a higher rate in patients receiving continuous rather than as-needed treatments [23, 66]. CATT additionally demonstrated higher rates of GA in patients receiving ranibizumab over bevacizumab [66]. This finding was not corroborated in the IVAN study, which demonstrated similar rates of GA between ranibizumab and bevacizumab [23]. This post hoc analysis of the data suggests that continuous anti-VEGF treatment may augment the rate of GA in patients with NVAMD. However, given that GA is part of the natural history of macular degeneration, it is difficult to establish causality, and further prospective studies specifically evaluating this will be required to confirm these initial findings.

Table 3 summarizes serious ocular adverse events in both the control and the treatment arms from the randomized clinical trials discussed in Tables 1 and 2. A review of the literature does not demonstrate a differential rate of serious ocular adverse events between drugs but suggests that ocular adverse events may vary based on technique. To minimize these complications, strict pre-injection precautions and proper technique are imperative.

3.5 Compounding Risk

Bevacizumab is the only drug of the four available anti-VEGF therapies that undergoes compounding before reaching the patient. This additional step in the manufacturer-to-patient sequence raises concerns about potential sterility if safe compounding methods are not carefully adhered to. In 2011, there was an outbreak of 12 streptococcus endophthalmitis cases after intravitreal bevacizumab [67] and eight cases of fungal endophthalmitis after combined triamcinolone–bevacizumab injections in 2012 [68].

Nonetheless, randomized clinical trials for the other three anti-VEGF agents demonstrate a similar rate of endophthalmitis to bevacizumab (Table 3). However, the randomized clinical trials often had significantly more controlled compounding procedures than found in standard clinical practice. Given the immense number of injections given, these cases are still rare [69]. Nonetheless, the severity of these cases illustrates the need for rigorous safety measures when compounding and transporting bevacizumab syringes to the healthcare providers.

3.6 Counterfeiting

Recently, Wang et al. [70] reported 80 of 116 patients who demonstrated a severe intraocular inflammation after receiving injections from three vials of counterfeit bevacizumab in Shanghai, China. This effect was confirmed to be endotoxin mediated. While nearly 80 % regained their pre-injection vision, the remainder demonstrated permanent vision loss of varying degrees. While this seems to be an isolated finding, this event emphasizes the importance of implementing stringent regulations and accountability standards for all compounding pharmacies.

3.7 Limitations

The randomized clinical trials discussed in this review were adequately designed and powered to detect clinical differences when evaluating the primary outcome of visual acuity letters gained or lost. However, the studies were not

Table 3 Major randomized control trials evaluating anti-vascular endothelial growth factor therapy for the treatment of exudative age-related macular degeneration: major ocular adverse events

Clinical trial (year published) and no. in each arm	Treatment group	Dose/injection/treatment regimen	Endophthalmitis	Uveitis	Retinal/subretinal/ vitreous hemorrhage	Retinal detachment	All major adverse events
VISION (2004) [13]							
298	–	Sham q6 weeks	–	–	–	–	–
295	PEG	0.3 mg q6 weeks	6 (2.0)	–	16 (1.8)[a]	1 (0.3)	–
301	PEG	1.0 mg q6 weeks	3 (1.0)	–		3 (1.0)	–
296	PEG	3.0 mg q6 weeks	3 (1.0)	–		2 (0.7)	–
MARINA (2006) [17]							
238	–	Sham monthly	0	0	2 (0.8)	1 (0.4)	33 (13.9)
238	RAN	0.3 mg monthly	2 (0.8)	3 (1.3)	1 (0.4)	0	40 (16.8)
240	RAN	0.5 mg monthly	3 (1.3)	3 (1.3)	1 (0.4)	0	59 (24.6)
ANCHOR (2009) [14]							
143	VER	Sham monthly injections + PDT	0	0	0	1 (0.7)	11 (7.7)
140	RAN	0.3 mg monthly + Sham PDT	0	0	2 (1.4)	2 (1.4)	10 (7.1)
140	RAN	0.5 mg monthly + Sham PDT	3 (2.1)	1 (0.7)	0	0	13 (9.3)
PIER (2010) [29]							
63	–	Sham monthly × 3, then quarterly (crossover in year 2 to monthly 0.5 mg RAN)	0	0	1 (1.6) sham	0	5 (7.9) sham
60	RAN	0.3 mg monthly × 3, then quarterly	0	0	1 (1.7)	0	6 (10.0)
61	RAN	0.5 mg monthly × 3, then quarterly	0	0	0	0	2 (3.3)
ABC (2010) [22]							
66	SC	PDT (for predominantly classic AMD) ($N = 16$) or PEG (for minimally classic or occult AMD) ($N = 38$) or sham treatment ($N = 12$)	0	1 (8.3) sham	0	1 (2.6) PEG	2 (5.3) PEG 1 (6.3) PDT 3 (25.0) sham
65	BEV	1.25 mg q6 weeks × 3, then q6 weeks PRN	0	2 (3.0)	1 (1.5)	0	11 (16.9)
EXCITE (2011) [31]							
120	RAN	0.3 mg monthly × 3, then quarterly	–[b]	–[b]	4 (3.3)	1 (0.8)	3 (2.5)
118	RAN	0.5 mg monthly × 3, the quarterly	–[b]	–[b]	8 (6.8)	0	5 (4.2)
115	RAN	0.3 mg monthly	–[b]	–[b]	2 (1.7)	0	1 (0.9)
CATT (2012) [24]							
301	RAN	0.5 mg monthly	4 (0.7)[a]	–	–	–	5 (0.8)[a]
	RAN	0.5 mg monthly (year 1); 0.5 mg PRN (year 2)					
298	RAN	0.5 mg PRN					
286	BEV	1.25 mg monthly	7 (1.2)[a]	–	–	–	8 (1.4)[a]
	BEV	1.25 mg monthly (year 1); 1.25 mg PRN (year 2)					
300	BEV	1.25 mg PRN					

Table 3 continued

Clinical trial (year published) and no. in each arm	Treatment group	Dose/injection/treatment regimen	Endophthalmitis	Uveitis	Retinal/subretinal/ vitreous hemorrhage	Retinal detachment	All major adverse events
MANTA (2013) [27]							
163	RAN	0.5 mg monthly × 3, then PRN	0	0	0	0	0
154	BEV	1.25 mg monthly × 3, then PRN	0	0	0	0	0
IVAN (2013) [23]							
157	RAN	0.5 mg monthly	–	0[a]	2 (0.6)[a]	1 (0.3)[a]	8 (2.6)[a]
155	RAN	0.5 mg monthly PRN					
149	BEV	1.25 mg monthly	–	1 (0.3)[a]	1 (0.3)[a]	0[a]	6 (2.0)[a]
145	BEV	1.25 mg monthly PRN					
GEFAL (2013) [26]							
239	RAN	0.5 mg monthly × 3, then PRN	1 (0.4)	–	1 (0.4)	0	6 (2.5)
246	BEV	1.25 mg monthly × 3, then PRN	0	–	0	0	2 (0.8)
VIEW 1/2 (2014) [37]							
595	RAN	0.5 mg monthly	5 (0.8)	–	4 (0.7)	3 (0.5)	26 (4.4)
613	AFL	2.0 mg monthly	4 (0.7)	–	3 (0.5)	1 (0.2)	22 (3.6)
601	AFL	0.5 mg monthly	1 (0.2)	–	5 (0.8)	2 (0.3)	19 (3.2)
610	AFL	2.0 mg monthly × 3, then q8 weeks	0	–	5 (0.8)	0	24 (3.9)
HARBOR (2014) [71]							
275	RAN	0.5 mg monthly	4 (1.5)	–	0	0	7 (2.5)
275	RAN	0.5 mg monthly × 3, then PRN	0	–	1 (0.4)	0	7 (2.5)
274	RAN	2.0 mg monthly	1 (0.4)	–	1 (0.4)	2 (0.7)	10 (3.6)
273	RAN	2.0 mg monthly × 3, then PRN	0	–	2 (0.7)	0	4 (1.5)
LUCAS (2015) [45]							
221	RAN	0.5 mg monthly until inactive, then extended × 2 weeks up to a maximum of 12 weeks	0 (0.0)	–	0 (0.0)	–	0 (0.0)
220	BEV	1.25 mg monthly until inactive, then extended × 2 weeks up to a maximum of 12 weeks	0 (0.0)	–	2 (0.9)	–	5 (2.3)

Data are presented as *N* (%) unless otherwise indicated

AFL aflibercept, *AMD* age-related macular degeneration, *BEV* bevacizumab, *PDT* photodynamic therapy, *PEG* pegaptanib, *PRN* pro re nata (as needed), *q* every, *RAN* ranibizumab, *SC* standard care, *VER* verteporfin, – indicates not reported or not identified

[a] Events for drug reported jointly

[b] Value not reported, but must have been ≤3 % per reporting standard of the study

powered to adequately assess differences in ocular and systemic adverse events between drug and sham or between anti-VEGF agents. As such, this review has compiled relevant literature on prospective data, meta-analysis, and large retrospective reports addressing safety. The results indicating no significant difference in adverse events is thus an extrapolated conclusion rather than a directly confirmed hypothesis. Additionally, the patient demographics of each study varied and may not represent the general population.

4 Conclusion

The last decade of anti-VEGF therapy has revolutionized the treatment of NVAMD. Since intravitreal pegaptanib first demonstrated clinical efficacy, anti-VEGF therapy has served as the mainstay treatment for NVAMD. Amongst the three leading anti-VEGF agents, clinical efficacy appears to be similar when evaluating visual acuity outcomes.

While there appears to be some differential in the magnitude of systemic VEGF suppression between the drugs, studies have not demonstrated differential rates of thromboembolic events or mortality when comparing anti-VEGF therapies. Additionally, rates of serious ocular adverse events do not appear to vary between different anti-VEGF therapies. To minimize these complications, safe pre-injection preparation and injection technique is advised.

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