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REVIEW ARTICLE

Comparison of adverse events of three anti-VEGF drugs for the treatment of age-related macular degeneration

Antonella Rosito[1], Silvia Caranti[1] and Roberto Verna[1,2,3,*]

[1]Research Center for Health and Social Wellness; [2]Academy for Health and Clinical Research; [3]World Association of Societies of Pathology and Laboratory Medicine

Abstract

Age-related macular degeneration (AMD) is one of the leading causes of irreversible central vision loss among elderly individuals in developed countries. The neovascular form of AMD is currently treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents, particularly ranibizumab, aflibercept, and bevacizumab. Although these therapies significantly improve visual outcomes, repeated intravitreal administration requires continuous monitoring of ocular and systemic adverse events. This review compares the safety profiles of the three principal anti-VEGF agents used for AMD treatment through analysis of pharmacovigilance data, regulatory reports, and major clinical trials. Particular attention is dedicated to ocular complications, systemic thromboembolic events, and the implications of off-label bevacizumab use. Current evidence suggests an overall comparable efficacy and safety profile among the three agents, although Bevacizumab requires stricter preparation and monitoring protocols because of its off-label use. Pharmacovigilance remains essential for identifying safety signals, supporting regulatory decisions, and optimising therapeutic strategies in ophthalmology.

Keywords: Age-related macular degeneration; Anti-VEGF; Ranibizumab; Aflibercept; Bevacizumab; Pharmacovigilance; Adverse events.

INTRODUCTION

Age-related macular degeneration (AMD) is a chronic and progressive retinal disease affecting the macula, the central portion of the retina responsible for high-resolution vision. AMD is currently the leading cause of irreversible visual impairment among individuals over 60 years of age in industrialized countries.[1] The disease is classified into two major clinical forms: dry (atrophic) AMD and wet (neovascular) AMD.[2] The neovascular form is less common but is responsible for the majority of severe visual loss cases because of choroidal neovascularisation, haemorrhage, retinal oedema, and fibrotic scarring.[3]

MATERIALS AND METHODS

This narrative review was conducted through a structured analysis of scientific literature, pharmacovigilance data, and regulatory documents concerning the safety of ranibizumab, aflibercept, and bevacizumab in neovascular age-related macular degeneration. The search was performed in PubMed, Embase, ClinicalTrials.gov, the European Medicines Agency website, and the EudraVigilance database, covering the period 2010–2024. Search terms included combinations of anti-VEGF agents, AMD, ocular and systemic adverse events, pharmacovigilance, and regulatory safety updates. Additional sources were identified by examining reference lists of relevant publications.

Studies were included if they reported safety outcomes for at least one of the three anti-VEGF agents and consisted of randomised trials, observational studies, systematic reviews, meta-analyses, pharmacovigilance assessments, or regulatory communications.

Non-peer-reviewed material, isolated case reports, and studies without safety data were excluded. Information extracted from each source included ocular and systemic adverse events, pharmacovigilance signals, and regulatory

**Address for correspondence:* Roberto Verna. Research Center for Health and Social Wellness, Guglielmo Marconi University, via Plinio 44, Roma, Italy. Tel: +393711547775; Email: *r.verna@unimarconi.it*

interventions. No new data were generated, and no statistical analyses were performed; findings were synthesized narratively. Ethics approval was not required, as the study did not involve human participants, biological samples, or experimental procedures. Reporting followed principles aligned with PRISMA-ScR, adapted to the narrative nature of the review.

AMD AND CURRENT THERAPEUTIC APPROACHES

Diagnosis

The diagnosis of AMD requires a complete ophthalmologic evaluation including optical coherence tomography (OCT), fluorescein angiography, indocyanine green angiography, and the Amsler grid test (Fig.1). OCT is considered the gold standard for detecting retinal oedema, drusen, and neovascular membranes, allowing clinicians to monitor disease progression and therapeutic response.[4]

Therapeutic strategies

Currently, no definitive treatment is available for dry AMD, although several preventive and therapeutic approaches may slow disease progression and preserve visual function. Lifestyle modifications remain essential and include smoking cessation, adherence to a diet rich in antioxidants and omega-3 fatty acids, protection from ultraviolet light exposure, and adequate control of cardiovascular risk factors such as hypertension and hyperlipidaemia. Nutraceutical supplementation based on the Age-Related Eye Disease Study (AREDS) and AREDS2 formulations have demonstrated beneficial effects in reducing disease progression in intermediate and advanced stages of AMD.[5] In particular, the AREDS2 formulation replaced beta-carotene with lutein and zeaxanthin because of the increased risk of lung cancer associated with beta-carotene in smokers.[6]

Several emerging therapeutic approaches are currently under investigation[7], including complement inhibitors such as pegcetacoplan and avacincaptad pegol, neuroprotective strategies, retinal pigment epithelium transplantation, and gene-based therapies aimed at reducing oxidative and exudative stress.[8] Visual rehabilitation also plays a fundamental role in improving patient quality of life through the use of magnifying devices, telescopic lenses, electronic aids, and structured low-vision rehabilitation programs.[9]

In contrast, neovascular AMD can be effectively treated with intravitreal anti-VEGF agents including ranibizumab, aflibercept,

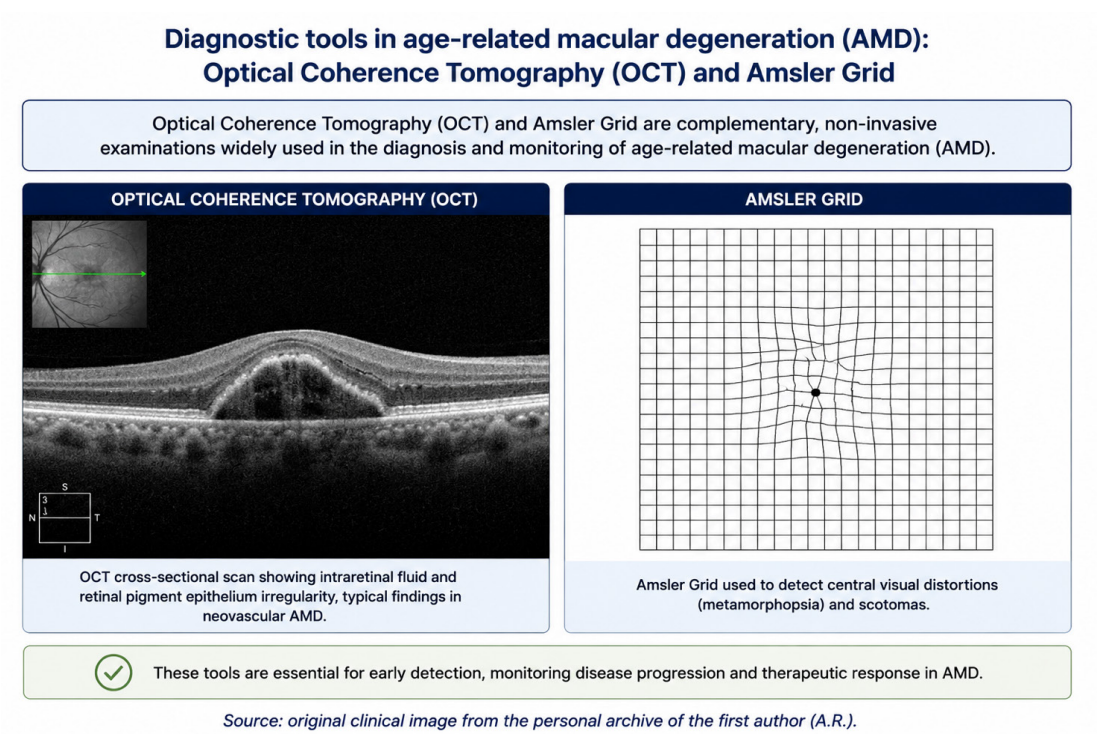

Figure 1. Diagnostics tools in age-related macular degeneration

and bevacizumab.[10] These therapies inhibit pathological angiogenesis and vascular permeability, thereby reducing retinal oedema and preserving visual acuity.[11]

Classification of ANTI-VEGF drugs

Anti-VEGF drugs used in the treatment of neovascular AMD belong to the class of monoclonal antibodies and soluble fusion receptor proteins designed to inhibit vascular endothelial growth factor (VEGF), thereby preventing receptor activation and pathological angiogenesis.

The main pharmacological characteristics, molecular targets, and major adverse events, associated with ranibizumab, aflibercept and bevacizumab are summarised in Table 1.

Ranibizumab is a humanised monoclonal antibody fragment specifically developed for intraocular administration and selectively targets

Table 1: Comparative pharmacological characteristics and major adverse events associated with anti-VEGF agents used in neovascular age-related macular degeneration (AMD)

Characteristic	Ranibizumab (Lucentis®)	Aflibercept (Eylea®)	Bevacizumab* (Avastin®)
Pharmacological features			
Molecular structure and type	Humanised monoclonal antibody (Fab fragment, 48 kDa)	Recombinant fusion protein (115 kDa)	Full-length humanised monoclonal antibody (149 kDa)
Molecular target	VEGF-A	VEGF-A, VEGF-B, PlGF	VEGF-A
Standard intravitreal dose in nAMD	0.5 mg/0.05 mL	2 mg/0.05 mL	1.25 mg/0.05 mL (off-label use)
Dosing regimen (after loading phase)	Pro re nata (PRN) or Treat-and-Extend (T&E)	Every 8 weeks (Q8W) or T&E	Pro re nata (PRN) or T&E
Intraocular half-life	~2.8 days	~4.3–5.8 days	~4.0–4.7 days
Duration of action	Shorter	Longer	Intermediate
Ocular adverse events (incidence)			
Endophthalmitis	Low (≈0.02–0.05%)	Low (≈0.02–0.05%)	Low (≈0.03–0.09%)
Retinal detachment	Low (≈0.1–0.6%)	Low (≈0.1–0.3%)	Low (≈0.2–0.4%)
Intraocular inflammation	Rare (<0.1–0.2%)	Rare (<0.1–0.2%)	Rare (0.1–0.2%)
Systemic adverse events (incidence)			
Arterial thromboembolic events (MI, stroke, systemic embolism)	Low (≈0.3–0.6%)	Low (≈0.5–1.1%)	Low (≈0.4–1.0%)
Hypertension	Low (≈0.6–1.1%)	Low (≈1.0–2.2%)	Low (≈1.1–2.5%)
All-cause mortality	~1.0%	~1.2%	~1.3%
Regulatory status in nAMD (Europe/Italy)	Approved	Approved	Not approved (off-label use) *
Key clinical considerations	• Extensive long-term safety data • Well-established efficacy • Favourable safety profile	• Longer duration may reduce treatment burden • Consider higher cardiovascular risk in fragile patients	• Cost-effective alternative • Requires compounding in hospital pharmacies and strict quality control

Abbreviations: nAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor; PlGF = placental growth factor; PRN = pro re nata; T&E = treat-and-extend; Q8W = every 8 weeks; MI = myocardial infarction.
*Bevacizumab is not approved for ophthalmic use in nAMD in Europe.
Source: Adapted with modifications from Korobelnik JF *et al*.[12]

VEGF-A isoforms. Aflibercept is a recombinant fusion protein acting as a soluble decoy receptor capable of binding VEGF-A, VEGF-B, and placental growth factor (PlGF), resulting in prolonged intravitreal activity and extended treatment intervals. Bevacizumab is a full-length monoclonal antibody directed against VEGF-A that was originally approved for oncologic indications and is currently widely used off-label in ophthalmology because of its comparable efficacy and lower cost relative to approved ophthalmic anti-VEGF agents.[3,6]

Mechanism of action of Anti-VEGF agents

VEGF plays a crucial role in the pathogenesis of neovascular AMD[3] by stimulating angiogenesis and increasing vascular permeability. Anti-VEGF agents inhibit VEGF signalling pathways and reduce pathological neovascularisation.

Ranibizumab is a recombinant humanised monoclonal antibody fragment specifically developed for intravitreal administration. It binds selectively to VEGF-A isoforms with high affinity, reducing retinal oedema and neovascular growth. Aflibercept is a recombinant fusion protein acting as a soluble decoy receptor for VEGF-A, VEGF-B, and placental growth factor (PlGF). Its broader binding profile and prolonged intravitreal activity may allow extended treatment intervals.[4] Bevacizumab is a full-length monoclonal antibody originally approved for oncologic indications. Despite its off-label status in ophthalmology, major studies such as CATT and IVAN demonstrated efficacy and safety profiles comparable to Ranibizumab.[3,6] However, Bevacizumab requires sterile aliquoting procedures before intravitreal use.

PHARMACOVIGILANCE ASPECTS OF ANTI-VEGF THERAPIES

Pharmacovigilance applied to intravitreal anti-VEGF therapies plays a crucial role in the clinical management of neovascular AMD.[11] Although these drugs have demonstrated significant efficacy in slowing disease progression and improving visual acuity, they are not free from ocular and systemic risks. Intravitreal injection of molecules such as ranibizumab, aflibercept, and bevacizumab requires careful post-administration clinical surveillance in order to promptly detect adverse events, monitor the long-term risk-benefit profile, and assess safety in off-label use[13], as in the case of bevacizumab (since it is not specifically formulated for ocular use, doses must be fractionated under sterile conditions, increasing the risk of contamination if procedures are not rigorous). Furthermore, frequent administration and the target population (generally elderly and with comorbidities) pose additional challenges for active pharmacovigilance. In this context, the role of regulatory authorities, healthcare facilities, and involved operators is fundamental to ensure effective collection, analysis, and management of adverse reaction reports, with the aim of ensuring safe, effective, and sustainable use of these innovative therapies.[14,15]

Ocular and systemic adverse reactions

Intravitreal administration of anti-VEGF agents is associated with both ocular and systemic adverse events related to the pharmacological properties of the molecules and to the injection procedure itself. Ocular adverse reactions include subconjunctival haemorrhage, transient increases in intraocular pressure, vitreous floaters, retinal detachment, intraocular inflammation, and endophthalmitis, the latter representing one of the most serious complications despite its relatively low incidence. Careful aseptic techniques and standardised injection protocols are therefore essential to minimise infectious risk.[16,17]

Systemic adverse events are less frequent but remain clinically relevant, particularly in elderly patients with cardiovascular comorbidities. Reported complications include arterial thromboembolic events such as stroke and myocardial infarction, hypertension, and vascular instability.[18] Although current evidence suggests comparable systemic safety profiles among ranibizumab, aflibercept, and bevacizumab, continuous pharmacovigilance and individualised patient assessment remain crucial for ensuring long-term therapeutic safety.[19,20]

Regulatory interventions and monitoring of the risk/benefit ratio

According to European pharmacovigilance regulations, all anti-VEGF administrations must be traceable and suspected adverse reactions must be appropriately reported. Particular attention is also paid to the off-label use of bevacizumab, which, despite having an efficacy profile comparable to other anti-VEGF drugs according to numerous studies (such as CATT and IVAN)[3,6], is not formally approved for intravitreal use. Regulatory authorities, through pharmacovigilance activities, continuously assess

safety data from clinical practice, highlighting the importance of careful monitoring of the risk/benefit ratio. When necessary, safety interventions have been adopted, such as revision of the Summary of Product Characteristics (SmPC), limitation of therapeutic indications, issuance of safety warnings, or recommendation of specific monitoring protocols. Active involvement of prescribers, through informational campaigns and periodic updates, and of patients, through spontaneous reporting and informed consent, is considered essential to maintain an acceptable risk profile and ensure long-term therapeutic effectiveness.

Monitoring the risk/benefit ratio of anti-VEGF drugs (ranibizumab, aflibercept, and bevacizumab) is of fundamental importance, especially in fragile populations such as the elderly. Following the collection of post-marketing data, some safety measures have become necessary. For example, regulatory authorities have recommended the use of single-use sterile needles and syringes to reduce the risk of endophthalmitis, and monitoring of intraocular pressure in patients at risk of glaucoma. For bevacizumab, used off-label, some health agencies have required the drafting of shared protocols regulating its intravitreal use, in order to limit uncontrolled use and ensure the quality of galenic preparations.

A concrete example of a national regulatory intervention designed to ensure the safe and appropriate use of anti-VEGF therapies is represented by Italian National Pharmacovigilance Network (AIFA) Note No. 98,[11] introduced through Determination No. DG/1379/2020 on December 28, 2020. This measure defines the criteria for prescribing and administering intravitreal ranibizumab, aflibercept, and bevacizumab within the Italian National Health Service. Notably, bevacizumab is included despite being used off-label for AMD, as it is authorised under Law 648/1996[11], which allows reimbursement for non-approved indications supported by solid scientific evidence and public health relevance. Note 98 establishes that such treatments must be performed exclusively in highly specialised hospital centres, previously approved by the Regions and equipped with protected outpatient clinics. This ensures not only suitable structural conditions for administration, but also proper treatment traceability and active surveillance of adverse events.

The technical document attached to the Note provides criteria for clinical appropriateness in therapeutic choice, based on evidence derived from registration studies (for ranibizumab and aflibercept)[3,4] and independent studies (for bevacizumab, such as the CATT and IVAN trials). It also emphasises the comparability of efficacy and safety profiles among the three drugs, thus authorising recourse to the most cost-effective treatment, always in compliance with the individual patient's clinical conditions.

Pharmacovigilance directed at these medicinal products is not limited to reporting adverse events, but also includes dynamic evaluation of the risk/benefit ratio, possible revision of the SmPC, and implementation of risk minimisation measures such as the use of sterile needles and syringes, monitoring of intraocular pressure, and standardised protocols for the preparation of bevacizumab by hospital pharmacies. The active involvement of prescribers is encouraged through regulatory tools and clinical guidelines, while the role of the patient is strengthened through informed consent and education on symptoms that should be reported promptly. This synergistic approach ensures not only the rational use of anti-VEGF drugs, but also effective and shared surveillance, an essential element of modern pharmacovigilance.

According to the summaries of the Risk Management Plans (RMPs) published by the European Medicines Agency (EMA), each drug is accompanied by the identification of the most relevant risks and the risk-minimisation measures necessary to reduce their impact.

Ranibizumab (Lucentis and biosimilars) is associated with important risks including endophthalmitis, intraocular inflammation, increased intraocular pressure, and retinal detachment. Potential risks include arterial thromboembolic events and immunogenicity. Risk-minimisation measures include routine measures (warnings in the SmPC, IOP monitoring, contraindications in the presence of ocular infections) and additional measures such as educational materials for clinicians and patient information leaflets.[8]

Aflibercept (Eylea and biosimilars) is associated with important risks overlapping with those of other anti-VEGF agents (endophthalmitis, intraocular inflammation, retinal detachment, increased IOP), with a potential risk of arterial thromboembolic events. In addition to routine measures, the EMA requires educational materials for physicians and information kits for patients.[9]

Bevacizumab (Avastin) has an EMA RMP concerning only intravenous oncological indications. The main risks include gastrointestinal perforations, haemorrhages, thromboembolic events, hypertension, proteinuria, and PRES. For oncological biosimilars, no additional measures beyond routine ones are foreseen. It is therefore important to underline that intravitreal use in AMD is off-label in Europe and not covered by the EMA RMP; consequently, risk management relies on national protocols (e.g., AIFA Note 98) and hospital sterile compounding procedures.[11,14]

This analysis highlights how the RMP, a cornerstone tool of pharmacovigilance, defines not only known and potential risks but also the minimisation strategies to be adopted, integrating post-marketing surveillance and supporting the safe use of these therapies in complex clinical settings.

RESULTS

Comparative Analysis of Safety Profiles and Clinical Implications

In the comparison among the safety profiles of the three main anti-VEGF drugs used in age-related macular degeneration—ranibizumab, aflibercept, and bevacizumab—data from the AIFA and the international literature show both critical issues and strengths from a safety perspective. A comparative overview of the major ocular and systemic adverse events, clinical considerations and principal evidence sources associated with anti-VEGF therapies is summarised in Table 2.[11,16,20]

Ocular adverse events

The frequency of severe ocular complications, such as endophthalmitis, retinal detachment, or intraocular inflammation, is low (<0.3%) for all drugs. However, bevacizumab shows a slightly higher risk (≈0.2–0.9%), probably related to off-label hospital preparation and the greater manipulation required during reconstitution in local pharmacies.[18]

Systemic adverse events

Comparative study[20] show no statistically significant differences between bevacizumab and ranibizumab in terms of thromboembolic events (myocardial infarction and stroke). However, a recent analysis suggests a slightly higher risk with aflibercept in patients with pre-existing cardiovascular conditions. According to AIFA data, rates of serious systemic events range around 0.6–0.7% for all three drugs, with no drug standing out significantly.

Focus on Bevacizumab (off-label)

Despite off-label use, bevacizumab demonstrates efficacy and a safety profile comparable to the other anti-VEGF drugs in the CATT and IVAN trials.[3,6] However, AIFA Note 98 recommends rigorous preparation protocols, sterile manipulation techniques, and enhanced clinical monitoring to reduce the risk of contamination and ocular ADRs.

DISCUSSION

Analysis and evaluation of the risk–benefit of therapies

The balance between clinical benefits and risks associated with anti-VEGF therapy is overall favourable for all three drugs.[3,4,5] Ranibizumab and aflibercept, thanks to their specific approval for ophthalmic use and greater standardisation in production and administration, are preferable in terms of formal safety. Bevacizumab, although less expensive, requires greater attention in preparation and administration, with rigorous protocols to reduce the risks of contamination and adverse reactions.[17]

Importance of pharmacovigilance in improving the safety and efficacy of treatments

Pharmacovigilance represents a fundamental tool in the management of anti-VEGF drugs, as it allows continuous and structured monitoring of long-term safety in a therapeutic context that involves repeated administrations, often in elderly and frail patients. The assessment of the risk–benefit ratio, central to pharmacovigilance, must be constantly updated based on post-marketing data and spontaneous reports of adverse reactions, with the aim of promptly detecting any risk signals not yet identified in registration trials and post-marketing phases. In the case of anti-VEGF drugs used in age-related macular degeneration, pharmacovigilance activity has led to the identification and management of several clinical issues. In particular: Reports of endophthalmitis associated with intravitreal injections have prompted the adoption of more rigorous aseptic protocols and the use of single-use sterile needles and syringes. This has significantly improved procedural safety, reducing the rate of serious infectious complications. The identification of systemic adverse events, such as thromboembolism and

Table 2: Comparative analysis of major ocular and systemic adverse events associated with anti-VEGF therapies in neovascular AMD: incidence from clinical trials, real-world studies and pharmacovigilance data

Drug	Major ocular adverse events (incidence %)	Major systemic adverse events (incidence %)	Clinical considerations	Main evidence / Source
Ranibizumab (Lucentis®)	•Endophthalmitis: 0.02–0.05% • Increased intraocular pressure: 0.1–0.6% • Retinal detachment: 0.1–0.2% • Intraocular inflammation: <0.1%	• Arterial thromboembolic events (MI, stroke, systemic embolism): 0.3–0.6% • Hypertension: 0.6–1.1% • All-cause mortality: ~1.0%	Extensive clinical experience and ophthalmic-approved formulation ensure a well-established safety profile with very low risk of severe ocular adverse events.	CATT; HORIZON; TREX-AMD; AIFA Pharmacovigilance Reports; SmPC Lucentis®
Aflibercept (Eylea®)	•Endophthalmitis: 0.02–0.05% • Increased intraocular pressure: 0.2–0.7% • Retinal detachment: 0.1–0.3% • Intraocular inflammation: 0.1–0.2%	• Arterial thromboembolic events (MI, stroke, systemic embolism): 0.5–1.1% • Hypertension: 1.0–2.2% • All-cause mortality: ~1.2%	Longer duration of action allows extended treatment intervals. A potential increased risk of arterial thromboembolic events has been observed in patients with pre-existing cardiovascular risk factors.	VIEW 1 & 2; ALTAIR; AIFA Pharmacovigilance Reports; SmPC Eylea®
Bevacizumab* (Avastin®)	•Endophthalmitis: 0.03–0.09% • Increased intraocular pressure: 0.3–0.9% • Retinal detachment: 0.2–0.4% • Intraocular inflammation: 0.1–0.2%	• Arterial thromboembolic events (MI, stroke, systemic embolism): 0.4–1.0% • Hypertension: 1.1–2.5% • All-cause mortality: ~1.3%	Off-label use in AMD. Safety profile comparable to other anti-VEGF agents, but requires compounding in hospital pharmacies, with a slightly higher risk of contamination-related events.	CATT; IVAN; AIFA Pharmacovigilance Reports; SmPC Avastin®

Abbreviations: AMD = age-related macular degeneration; anti-VEGF = anti-vascular endothelial growth factor; MI = myocardial infarction; SmPC = Summary of Product Characteristics; AIFA = Italian National Pharmacovigilance Network
*Bevacizumab is not approved for ophthalmic use in nAMD in Europe.
Source: Adapted and modified from Korobelnik JF *et al*.[12]; Martin DF *et al*.[3]; Heier JS *et al*.[4]

transient increases in intraocular pressure, has led to recommendations for clinical monitoring and greater attention in treating patients with cardiovascular comorbidities.[19,20] In the case of bevacizumab, off-label use has required particular attention to the quality of galenic preparation, with specific guidelines on handling and vial fractionation to minimise the risk of contamination and molecular instability.

Pharmacovigilance has also played a key role in identifying potential differences among available molecules, helping to guide therapeutic and regulatory decisions. For example, the review of safety data supported the development of AIFA Note 98[11], which affirms the equivalence in terms of efficacy and tolerability of the three main anti-VEGF agents (ranibizumab, aflibercept, bevacizumab), while highlighting the need for an adequate organizational context for the safe use of the latter. Another relevant aspect concerns the active involvement of prescribers in pharmacovigilance: physicians not

only administer treatment but also participate in the systematic collection of information on adverse events and collaborate with regulatory authorities to update indications for use. Continuous training of clinical operators and the availability of digital tools for reporting have improved the accessibility and effectiveness of the national pharmacovigilance system.

The role of the patient is also becoming increasingly central: through information and informed consent, patients can actively contribute to the early detection of ADRs by reporting unusual symptoms or post-administration effects. This collaborative approach, based on transparency and risk sharing, is now considered a strategic element for optimising therapy, especially in high-impact clinical settings such as geriatric ophthalmology. In conclusion, pharmacovigilance in anti-VEGF treatments is not only a control tool, but also a lever for quality and sustainability within the healthcare system. It allows clinical recommendations to be adapted over time, improves patient safety, and contributes to therapeutic practice grounded in evidence and shared responsibility.

Future perspectives and new approaches

Future developments in the treatment of neovascular AMD are expected to focus on therapies capable of extending treatment intervals and reducing the burden associated with repeated intravitreal injections. Long-acting anti-VEGF molecules, port delivery systems, and sustained-release implants are currently under investigation and may significantly improve patient adherence and quality of life. In addition, advances in gene therapy and RNA-based therapeutic approaches could provide more durable suppression of VEGF activity.[19]

The integration of artificial intelligence and digital pharmacovigilance tools is also expected to improve the early identification of safety signals and optimise individualised therapeutic strategies. Real-world evidence databases and automated monitoring systems may contribute to a more proactive and personalized management of AMD, particularly in elderly and fragile populations.[20]

The comparative evaluation of ranibizumab, aflibercept, and bevacizumab demonstrates that all three anti-VEGF agents provide substantial therapeutic benefits in the management of neovascular AMD, with overall comparable efficacy and safety profiles. Ranibizumab and aflibercept benefit from formal ophthalmologic approval, standardised production, and well-established administration protocols, whereas bevacizumab continues to represent a cost-effective off-label alternative with comparable clinical performance.[2,5,9]

Nevertheless, the off-label use of bevacizumab requires stricter preparation protocols and careful monitoring to minimise contamination risks and ensure patient safety. Pharmacovigilance therefore plays a strategic role in monitoring long-term safety, detecting emerging adverse events, supporting regulatory decisions, and improving the risk-benefit assessment of anti-VEGF therapies.[11,16,20]

In conclusion, therapeutic decisions should be individualised according to patient characteristics, clinical status, comorbidities, and local regulatory frameworks. Continuous pharmacovigilance, real-world evidence collection, and multidisciplinary collaboration remain essential for optimising the safe and effective use of anti-VEGF therapies in ophthalmology.

CONCLUSIONS

Anti-VEGF therapy has revolutionized the treatment of neovascular age-related macular degeneration, significantly improving visual prognosis and patients' quality of life. Current evidence supports comparable efficacy and overall safety profiles among ranibizumab, aflibercept, and bevacizumab, although the latter requires stricter preparation protocols and enhanced monitoring because of its off-label intravitreal use.[3,4,10,11]

A schematic overview summarising the principal mechanism of action, adverse events, and clinical implication of anti-VEGF therapies is presented in Figure 2.

Pharmacovigilance therefore remains essential for identifying emerging safety signals, optimising the risk–benefit assessment of therapies, and supporting regulatory decision-making in clinical practice.[11,15,19]

Continuous monitoring, standardised reporting systems, and multidisciplinary collaboration are crucial to ensure the safe and effective long-term management of patients with AMD. Future integration of pharmacovigilance systems, real-world evidence, artificial intelligence tools, and personalised therapeutic approaches will likely play a pivotal role in optimising treatment safety, efficacy, and sustainability in modern ophthalmology.[19,20,21]

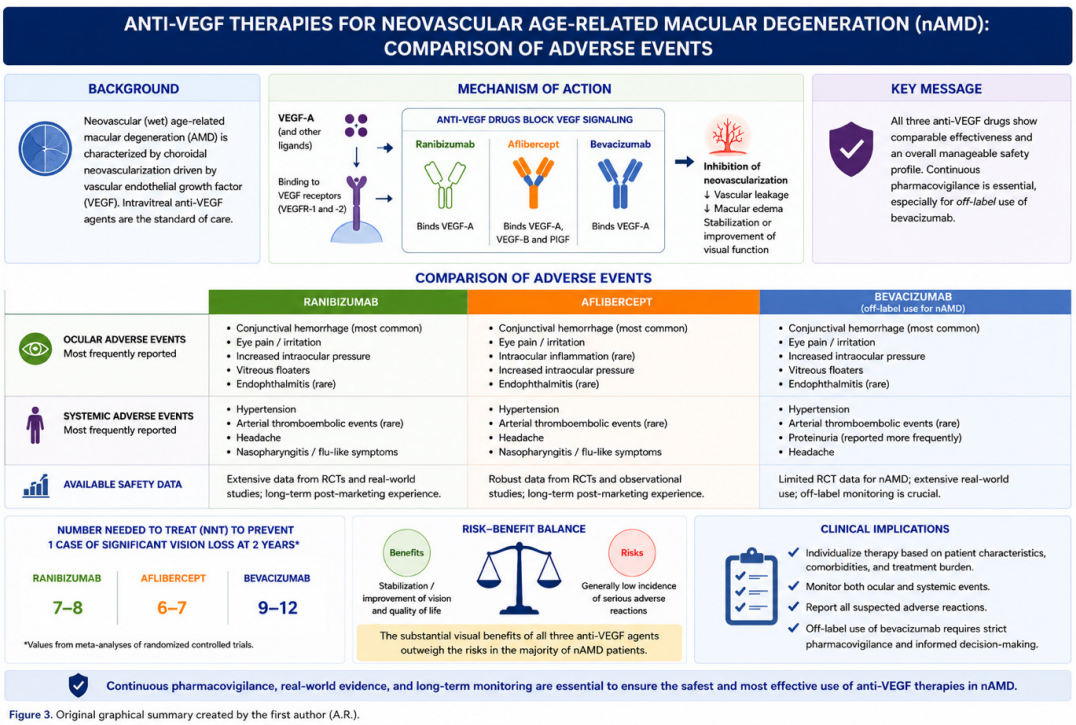

Figure 3. Original graphical summary created by the first author (A.R.).

Figure 2. Schematic overview of anti-VEGF therapies

Conflict of interest: The authors declare no conflict of interest.

REFERENCES

1. Wong WL, Su X, Li X, *et al*. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014; 2:e106-16.
2. Ferris FL 3rd, Wilkinson CP, Bird A, *et al*. Clinical classification of age-related macular degeneration. Ophthalmology. 2013; 120:844-51.
3. Martin DF, Maguire MG, Ying GS, *et al*. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011; 364:1897-908.
4. Heier JS, Brown DM, Chong V, *et al*. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology. 2012; 119:2537-48.
5. Rosenfeld PJ, Brown DM, Heier JS, *et al*. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006; 355:1419-31.
6. Chakravarthy U, Harding SP, Rogers CA, *et al*. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet. 2013; 382:1258-67.
7. Schmitz-Valckenberg S, Fleckenstein M, Göbel AP, Hohman TC, Holz FG. Optical coherence tomography and autofluorescence findings in areas with geographic atrophy due to age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52(1):1-6.
8. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. 2001; 119:1417-36.
9. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA. 2013; 309:2005-15.
10. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2019; 3(3):CD005139.
11. Italian Medicines Agency (AIFA). AIFA Note no. 98 – Prescription and intravitreal administration of anti-VEGF medicinal products. Official Gazette of the Italian Republic. 2020 Dec 31;322.
12. Korobelnik JF, Holz FG, Roider J, *et al*. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology. 2014;121(1):193-201.
13. European Medicines Agency (EMA). Lucentis: EPAR – Risk Management Plan. EMA; 2023.
14. European Medicines Agency (EMA). Eylea: EPAR – Risk Management Plan. EMA; 2025.

15. European Medicines Agency (EMA). Avastin: EPAR – Risk Management Plan. EMA; 2025.
16. Banerjee M, Moharana S, Padhy SK. Systemic Effects of Intravitreal Anti-VEGF Therapy: A Review of Safety across Organ Systems. *Ophthalmol Ther*. 2025;14(8):1661-1684.
17. Maloney MH, Schilz SR, Herrin J, Sangaralingham LR, Shah ND, Barkmeier AJ. Risk of Systemic Adverse Events Associated with Intravitreal Anti-VEGF Therapy for Diabetic Macular Edema in Routine Clinical Practice. Ophthalmology. 2019;126(7):1007-1015.
18. Bhavsar AR, Stockdale CR, Ferris FL 3rd, *et al*. Update on risk of endophthalmitis after intravitreal drug injections and potential impact of elimination of topical antibiotics. Arch Ophthalmol. 2012;130(6):809-810.
19. Lin TY, Hsieh YT, Garg SJ, *et al*. Systemic effects of anti-VEGF intravitreal injection in patients with age-related macular degeneration: A multi-institutional real-world study. Indian J Ophthalmol. 2024;72(Suppl 5):S809-S815.
20. Thulliez M, Angoulvant D, Pisella PJ, Bejan-Angoulvant T. Overview of Systematic Reviews and Meta-analyses on Systemic Adverse Events Associated With Intravitreal Anti-Vascular Endothelial Growth Factor Medication Use. JAMA Ophthalmol. 2018;136(5):557-566.
21. Avery RL, Castellarin AA, Steinle NC, *et al*. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. Retina. 2014;34(5):790–798.