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REVIEW

Efficacy and Safety of Aflibercept Biosimilars Relative to Reference Aflibercept Therapy for Neovascular Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis

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Purpose: To assess the efficacy and safety of aflibercept biosimilars compared to reference aflibercept therapy for neovascular age-related macular degeneration (nAMD) through a systematic review and meta-analysis.

Methods: A comprehensive literature search was conducted across multiple databases. Randomized controlled trials comparing intravitreal aflibercept biosimilars with reference aflibercept in patients with nAMD were included. The outcomes were changes in best-corrected visual acuity (BCVA), retinal thickness, choroidal neovascularization (CNV) leakage area from baseline based on fluorescein angiography, and adverse events.

Results: Five studies involving 2,039 patients were included. No statistically significant differences were found between aflibercept biosimilars and reference aflibercept in terms of BCVA (weighted mean difference [WMD]: 1.05; 95% CI: −0.62 to 2.71; p = 0.22), central subfield thickness (WMD: 3.33; 95% CI: −14.48 to 21.14; p = 0.71), or CNV (WMD: −0.23; 95% CI: −0.58 to 0.12; p = 0.20). SThe incidence of treatment-emergent adverse events was similar between groups.

Conclusion: Aflibercept biosimilars demonstrated comparable efficacy and safety profiles to reference aflibercept in the treatment of nAMD. These findings suggest that biosimilars may serve as a cost-effective alternative without compromising patient outcomes.

Keywords: neovascular age-related macular degeneration, nAMD, aflibercept, biosimilars, anti-VEGF therapy, efficacy, safety

Introduction

Age related macular degeneration (AMD) is major cause of visual disability in elderly population globally.[1] By 2040, the global prevalence of AMD is anticipated to rise to approximately 288 million individuals.[2] Vision loss in AMD is primarily caused by choroidal neovascularization (CNV), a process driven by vascular endothelial growth factor (VEGF), which plays a pivotal role in the development of neovascularization in patients with neovascular AMD (nAMD).[3]

Laser surgery, photodynamic therapy, and anti-VEGF are considered current treatment options for nAMD.[4] The gold standard for nAMD is repeated intravitreal anti-VEGF injections.[4–7] The frequently utilized anti-VEGF agents include Ranibizumab, Aflibercept, the off-label use of Bevacizumab, and the emerging use of Faricimab.[8,9] Aflibercept, in particular, is a widely utilized anti-VEGF therapy that binds to VEGF receptors and placental growth factor to inhibit neovascularization.[10] While these therapies have revolutionized nAMD management, their high cost poses a significant financial burden on patients and healthcare

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systems. This highlights the urgent need for effective and affordable alternatives to improve accessibility without compromising treatment outcomes.[11]

A biosimilar is a biological product that is highly similar to an approved reference drug in terms of chemical, physical, and biologic features. Moreover, it is similar in terms of safety, efficacy, and immunogenicity, and it has been shown to decrease cost.[12,13] The original patents for aflibercept expired in 2023 in the United States and are set to expire in 2025 in Europe, allowing for the introduction of biosimilar in these market.[14] There are different Aflibercept biosimilars at various stages of development and approval. Currently, there are no standardized international guidelines for biosimilar in clinical medical practice. For this reason, guidelines may vary across countries and evolve over time with advancements in technology.[14] Therefore, the aim of this systematic review and meta-analysis is to assess and compare the effectiveness and safety of Aflibercept biosimilar to the reference Aflibercept anti-VEGF therapy for the treatment of nAMD.

Materials and Methods

Literature Search Strategy

A systematic review and meta-analysis, registered with PROSPERO (ID:CRD42024587507), were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study screening process for the included studies of this meta-analysis is illustrated in Figure 1. The following electronic databases were comprehensively searched: Pubmed Central, Ovid MEDLINE Cochrane Library, Scopus, Registry of controlled Trials, Web of Science, Directory of Open Access Journal Databases; using relevant keywords "Wet Macular Degeneration" "neovascular age-related macular degeneration", "nAMD", "Biosimilar Pharmaceuticals", "Biosimilar aflibercept", " Reference aflibercept", from inception till 26 September 2024. All published articles were considered with no restrictions in terms of language or publication period. Further, we manually scanned the bibliography of retrieved articles for additional relevant studies.

Eligibility Criteria and Study Selection

We included studies with the following criteria: (a) randomized controlled trials (RCTs) that compared intravitreal Aflibercept biosimilars with reference Aflibercept; (b) patients > 18 yrs; (c) untreated subfoveal choroidal neovascu larization (CNV) secondary to nAMD; (d) reported data on any of the following outcomes: best-corrected visual acuity (BCVA), central subfield thickness (CST), Central Macular Thickness (CMT), Total Retinal Thickness (TRT), choroidal neovascularization (CNV) at various weeks endpoints. Articles were excluded if: (1) non-randomized controlled trials or comparative interventional case series; (2) studies that compared intravitreal ranibizumab biosimilars or reference ranibizumab with different intervention; (3) CNV secondary to other reasons. Duplicates were removed using Mendeley software and retrieved references were screened in two stepwise manner: titles/abstracts screening for matching our inclusion criteria, followed by a full-text appraisal of relevant articles for eligibility to meta-analysis. Each step was performed by two independent reviewers.

Data Extraction

Each type of dataset was extracted independently by two authors. Discrepancies were settled through discussion and consensus among the reviewers. The extracted data involved the study ID (name of the first author and year of publication), location, study design, number, sex, and age for each intervention arm of enrolled patients, biosimilar name, treatment outcome measures, and adverse events between treatment arms. We did not estimate values from figures and only included data explicitly reported in the text or received directly from the authors.

Data Synthesis and Quality Assessment

The outcomes of interest were changes in BCVA from baseline, changes in retinal thickness from baseline, changes in CNV leakage area from baseline based on fluorescein angiography. These measurements were extracted at baseline and at the final follow-up, which varied among studies. Li et al and Kang et al reported final measurements at 52 weeks, while Sadda et al provided data at 56 weeks.[14–16] Additionally, adverse events data were also extracted. It's important to

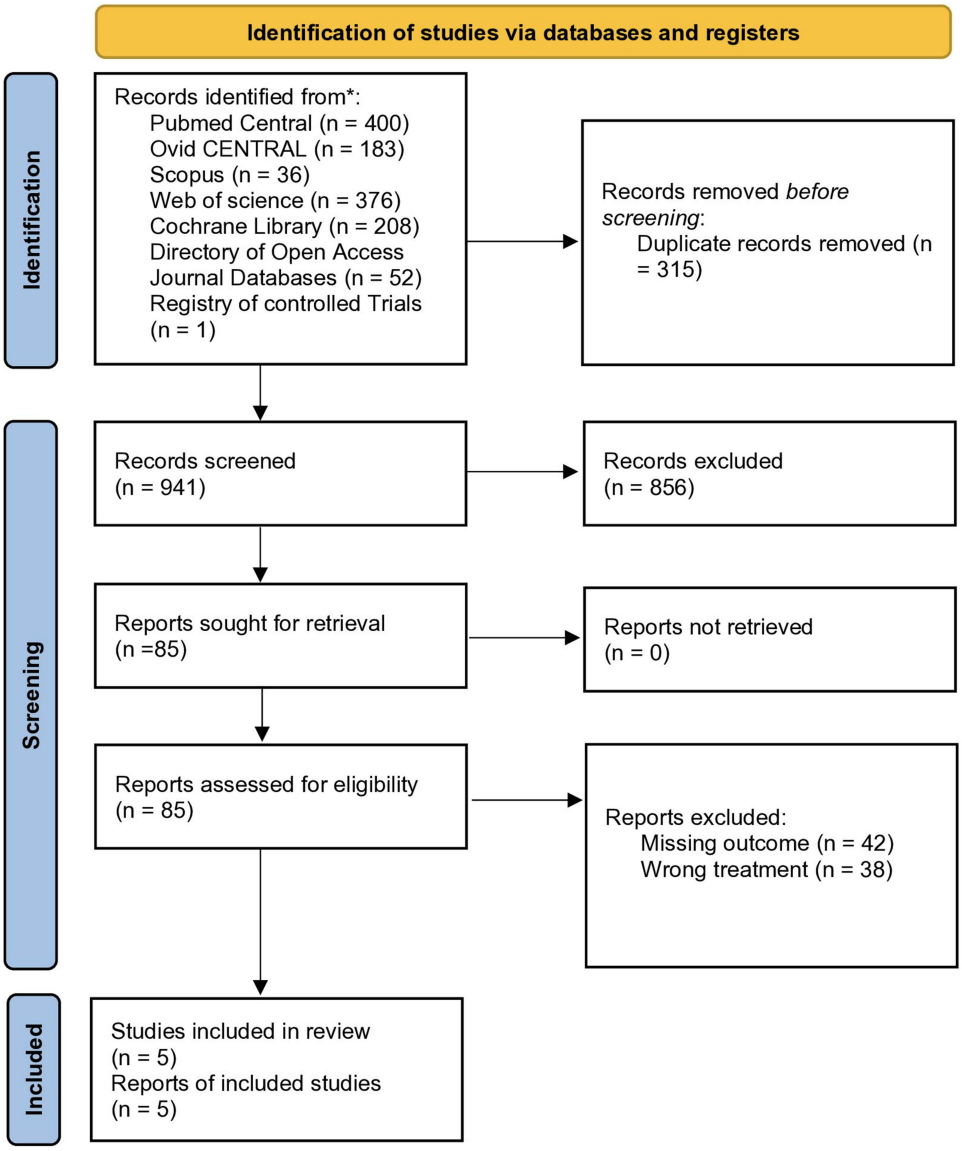

Figure 1 PRISMA flowchart for articles screening process.

note that data reporting methods differed across studies. Karkhaneh et al and Bordon et al presented their results using mean and standard deviation, whereas Li et al, Kang et al, and Sadda et al employed different reporting methods. Consequently, for Karkhaneh et al and Bordon et al, we only collected data on adverse events, excluding them from the analysis of changes in BCVA, retinal thickness, and CNV leakage area from baseline, which were analyzed for the remaining three studies.[14–18]

Two independent authors assessed the risk of bias and certainty of evidence with conflicts resolved through a third independent author. To assess the risk of bias and certainty of evidence of the included studies, we used Cochrane's Risk of Bias tool 2 (ROB2).[19]

Statistical Analysis

Stata (StataCorp. 2024) was used for all statistical analyses. Continuous variables were presented as weighted means (effect size of means) with 95% confidence intervals (CIs), while categorical variables were presented as logit-transformed proportions (effect size of proportions) with 95% CIs. All meta-analyses were conducted using a random-effects model.[20,21] Subgroup meta-analyses of weighted means with 95% CIs and logit-transformed proportions with

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95% CIs were performed to assess differences in demographics and adverse events among the groups.[22,23] For clinical outcomes, least squared means were reported in all of the included trials, which were then converted to mean differences and pooled into a single weighted mean difference, representing the overall outcome value. Heterogeneity among studies was evaluated using the Chi-square ($\chi 2$) test and the Higgins I2 test.[24] A two-tailed p-value of <0.05 was considered statistically significant for all statistical analyses. Egger's test in addition to funnel plots were used to assess publication bias among the included trials, and no bias was detected (Supplementary Figure 1).[25]

Results

Study Selection

The initial literature search of databases returned a total of 1256 articles (Figure 1). After eliminating duplicates, 941 articles left. Through titles and abstracts screening, 856 studies were excluded. 85 papers were then retrieved for full-text review. Ultimately, 80 articles did not meet the inclusion criteria and were excluded. Therefore, 5 articles, categorized as level II evidence, were included in the analysis.[14–18]

Two independent reviewers, J.Q. and R.H., utilized the RoB 2 tool.[19] to systematically assess the potential risk of bias in the included randomized controlled trials (RCTs).[14–18] Any discrepancies between reviewers were resolved through discussion until consensus was achieved. Among the five trials evaluated, three were determined to have a low risk of bias, while two were identified as having some concerns (see Supplementary Figure 2).

Demographic Characteristics

Our cohort included a total of 2,039 patients diagnosed with neovascular age-related macular degeneration, who received either reference Aflibercept (n = 1,016, 49.8%) or Aflibercept biosimilars (n = 1,023; 50.2%). The weighted mean age was 71.4 years (95% CI: 64.7–78.0) in the reference Aflibercept group and 71.8 years (95% CI: 64.9–78.7) in the biosimilars group (p = 0.93). The distribution of sex was nearly equal in both groups, with a slightly higher prevalence of males in each [reference Aflibercept: 51.7% (95% CI: 41.3% – 62.0%) and biosimilars: 54.5% (95% CI: 44.2% – 64.5%), p = 0.71; Table 1).

Table 1 Demographic and Clinical Characteristics of the Cohort

Variable	Reference Aflibercept (n = 1,016)	Aflibercept Biosimilars (n = 1,023)	*p*-value
Age	71.4 (64.7–78.0)	71.8 (64.9–78.7)	0.93
Sex			
Female	48.3% (38.0% – 58.7%)	45.5% (35.5% – 55.8%)	0.36
Male	51.7% (41.3% – 62.0%)	54.5% (44.2% – 64.5%)	0.71
TEAEs			
Ocular	22.1% (12.8% – 35.4%)	23.8% (14.8% – 35.9%)	0.83
Non-ocular	17.9% (8.20% – 34.8%)	19.2% (9.10% – 36.1%)	0.89
Decreased visual acuity	1.90% (0.70% – 5.40%)	3.70% (2.40% – 5.50%)	0.25
Conjunctival hemorrhage	2.80% (1.10% – 6.80%)	4.20% (2.70% – 6.40%)	0.44
Retinal hemorrhage	0.80% (0.30% – 2.30%)	1.10% (0.60% – 2.10%)	0.64
Cataract	1.60% (0.90% – 2.90%)	1.50% (0.80% – 2.90%)	0.89
Eye pain	2.30% (0.30% – 17.1%)	3.80% (1.0% – 13.2%)	0.69
Arterial thromboembolism events	0.70% (0.30% – 1.60%)	1.80% (1.0% – 3.30%)	0.06
Mortality	0.30% (0.10% – 1.10%)	0.60% (0.10% – 2.60%)	0.58

Notes: All data are reported as weighted means (95% confidence intervals) or logit-proportions % (95% confidence intervals), derived from meta-analyses.
Abbreviation: TEAEs, treatment-emergent adverse events.

Clinical Outcomes of Reference Aflibercept Vs Biosimilars

In the meta-analysis, the weighted mean difference (WMD) — which represents the average difference in outcomes between intervention and control groups, weighted by the inverse of each study's variance—was used to assess treatment effects. The BCVA from baseline to week 52 or 56 across the included trials was 1.05 (95% CI: −0.62 to 2.71, p = 0.22), supporting the comparability of reference Aflibercept and its biosimilars. There was no significant heterogeneity observed (p = 0.63), which strengthens the reliability of these findings (Figure 2). Similarly, there was no statistically significant difference in central subfield thickness between the two groups [WMD: 3.33 (95% CI: −14.48 to 21.14), p = 0.71; Figure 3]. For choroidal neovascularization, the meta-analysis also demonstrated no significant difference between reference Aflibercept and its biosimilars [WMD: −0.23 (95% CI: −0.58 to 0.12), p = 0.20; Figure 4]. There was no significant heterogeneity across the included trials (p = 0.91), further emphasizing the reliability of these findings.

Adverse Events

No statistically significant differences were observed in treatment-emergent adverse events (TEAEs) between the reference Aflibercept and biosimilars groups (Table 1). Ocular TEAEs were the most commonly reported in both groups [reference Aflibercept: 22.1% (95% CI: 12.8% – 35.4%) and biosimilars: 23.8% (95% CI: 14.8% – 35.9%), p = 0.83]. Non-ocular TEAEs followed as the second most common events [reference Aflibercept: 17.9% (95% CI: 8.20% – 34.8%) and biosimilars: 19.2% (95% CI: 9.10% – 36.1%), p = 0.89]. Other adverse events, such as decreased visual acuity, conjunctival or retinal hemorrhage, cataract, eye pain, arterial thromboembolism, and mortality, were less commonly

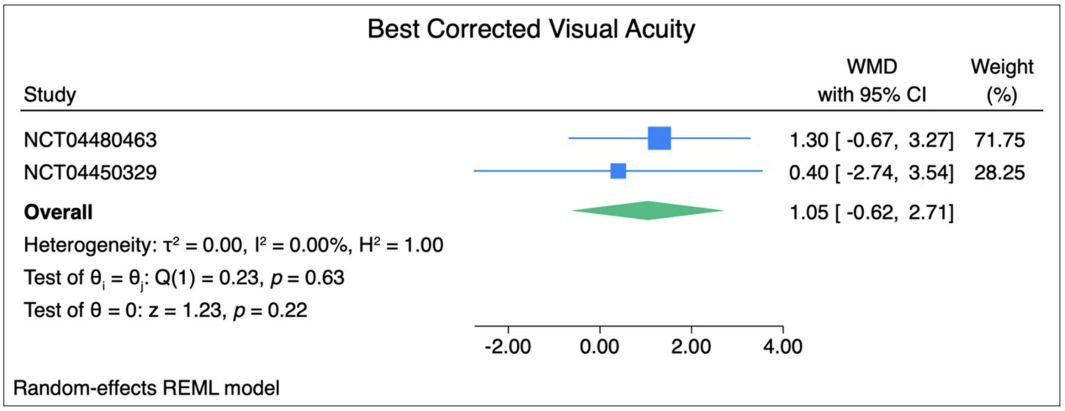

Figure 2 Forest plots of weighted mean difference (WMD) for best corrected visual acuity outcomes.
Abbreviations: NCT, national clinical trial; CI, confidence interval.

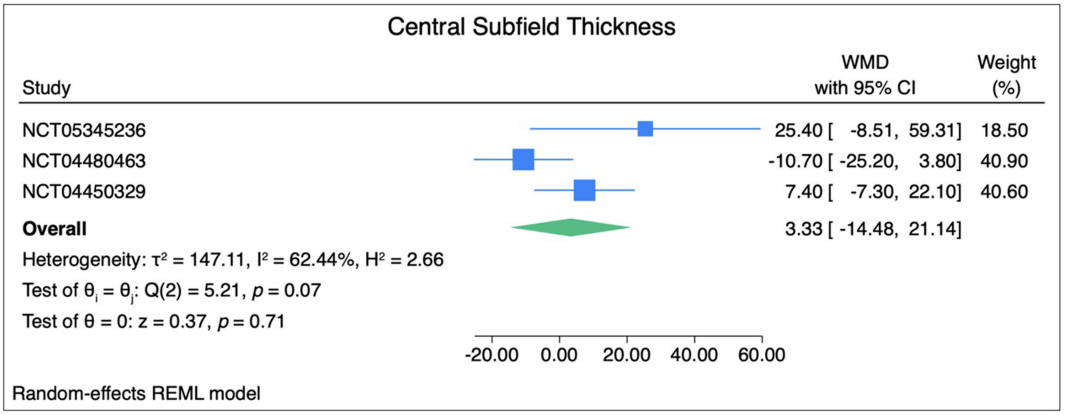

Figure 3 Forest plots of weighted mean difference (WMD) for central subfield thickness outcomes.
Abbreviations: NCT, national clinical trial; CI, confidence interval.

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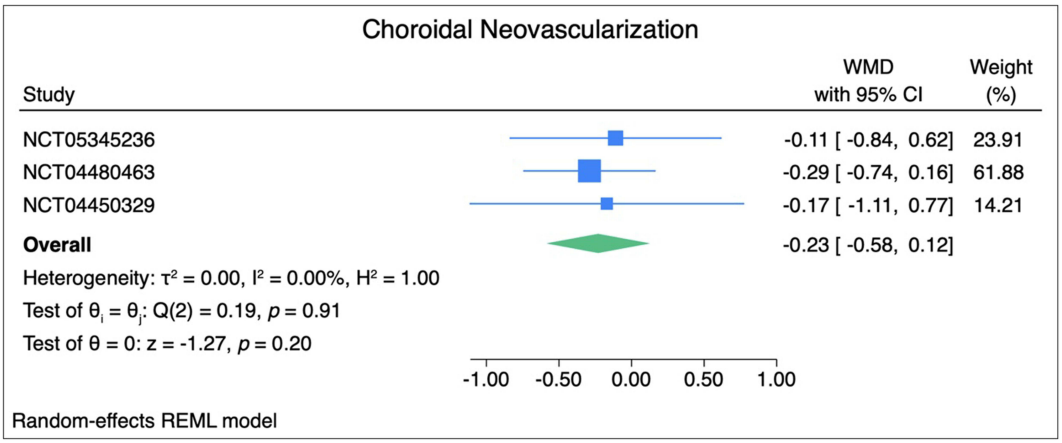

Figure 4 Forest plots of weighted mean difference (WMD) for choroidal neovascularization outcomes.
Abbreviations: NCT, national clinical trial; CI, confidence interval.

reported in both groups (Table 1). A total of three cases of endophthalmitis were reported in the studies, two occurring in both treatment arms and one exclusively in the biosimilar arm. Intraocular inflammation was less frequent, with two cases reported, all in the reference group.[14–18]

Discussion

Age-related macular degeneration (AMD) is still the leading cause of visual impairment in the elderly population worldwide, with nAMD triggered primarily but not exclusively by VEGF-mediated choroidal neovascularization.[1] Intravitreal anti-VEGF injection, including Aflibercept, have been the mainstay therapy of nAMD management.[4–7] Aflibercept's efficacy and safety were were well established in VIEW study.[26] However, due to their high cost it is not universally available and accessible.[11] This highlights the importance of the Biosimilars. Currently, few biosimilars to Aflibercept (Eylea) have been developed and approved worldwide, including FDA-approved biosimilars such as Yesafili, Opuviz (SB15), Ahzantive (FYB203), Enzeevu, and Pavblu.[27] Moreover, European commission – approved biosimilars include Yesafili, Opuviz (SB15), and Afqlir.[28] We included as well the biosimilar QL1207, which developed by Qilu Pharmaceutical in China. This study aimed to assess the clinical effectiveness and safety of these Aflibercept biosimilars compared to reference Aflibercept in managing nAMD. The findings of this study demonstrate the clinical equivalence of reference Aflibercept and its biosimilars in the treatment of neovascular age-related macular degeneration (nAMD). The occurrence of treatment-emergent adverse events (TEAEs) was similar between the two groups. Ocular TEAEs, the most commonly reported events, occurred in approximately 22–24% of patients, and non-ocular TEAEs were reported in approximately 18–19% of patients, both demonstrate no statistically significant differences. Other serious adverse events, including decreased visual acuity, conjunctival or retinal hemorrhage, and arterial thromboembolism, were rare in both groups. These findings suggest that biosimilars share a similar safety profile with reference Aflibercept, consistent with prior post-marketing surveillance studies. Our meta-analysis demonstrates that biosimilars and reference Aflibercept show comparable visual and anatomical outcomes in the treatment of nAMD. There were no significant differences in best-corrected visual acuity, central subfield thickness, or choroidal neovascularization outcomes. The absence of heterogeneity across trials enhances the reliability and applicability of these findings.

The availability of biosimilars for anti-VEGF therapy has significant implications for clinical practice. The comparable efficacy and safety profiles observed in this study suggest that biosimilars can be integrated into routine clinical practice as a cost-effective alternative to reference Aflibercept in the treatment of nAMD without compromising patient outcomes.

While this study provides valuable insights into the comparability of reference Aflibercept and its biosimilars, some limitations warrant consideration. First, not only one type of Aflibercept biosimilar was used in the included study, so this could affect the generalisability of our results. Also, the short follow-up period (52 to 56 weeks) may not detect potential long-term differences in safety or efficacy. Further research, including randomized controlled trials and real-world studies

with extended follow-up, is needed to confirm the long-term safety and efficacy of biosimilars in diverse patient populations. Post-marketing surveillance programs are also essential to increase the confidence in the use of biosimilars. These results contribute to the growing body of evidence supporting the use of Aflibercept biosimilars as a safe and effective alternative to the reference product.

Conclusion

This systematic review and meta-analysis provide evidence supporting the clinical equivalence of aflibercept biosimilars to reference aflibercept in the treatment of neovascular age-related macular degeneration. The comparable efficacy in terms of visual acuity, retinal thickness, and choroidal neovascularization, along with similar safety profiles, suggests that an aflibercept biosimilars can be integrated into routine clinical practice as a cost-effective alternative. These findings contribute to the growing body of evidence supporting the use of aflibercept biosimilars as a safe and effective alternative to the reference product in nAMD management.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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