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Comparative Efficacy and Safety of Anti-VEGF Agents in Neovascular Age-Related Macular Degeneration: A Meta-Analysis

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A B S T R A C T

Neovascular age-related macular degeneration (nAMD) is a leading cause of vision loss in the elderly. This meta-analysis aims to compare the efficacy and safety of various anti-VEGF agents, including ranibizumab, bevacizumab, aflibercept, and brolucizumab, in the treatment of nAMD. A comprehensive understanding of the comparative effectiveness of these agents is crucial for informing clinical decision-making and optimizing treatment strategies. A meta-analysis was conducted using electronic databases, including PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), to identify relevant randomized controlled trials (RCTs) published between 2013 and 2024. The search strategy involved a combination of Medical Subject Headings (MeSH) terms and keywords. Two independent reviewers extracted data from the included studies using a standardized form. The extracted data included study characteristics, patient demographics, treatment details, visual acuity outcomes, and safety profiles. Seven RCTs were included in the meta-analysis. The analysis revealed that all anti-VEGF agents resulted in significant improvements in visual acuity compared to control. Notably, aflibercept and brolucizumab demonstrated greater improvements in visual acuity at 12 months compared to ranibizumab and bevacizumab. The incidence of ocular adverse events, including endophthalmitis, intraocular inflammation, and retinal detachment, was similar across the anti-VEGF agents. All anti-VEGF agents are effective in improving visual acuity in nAMD. Aflibercept and brolucizumab may offer superior visual acuity outcomes compared to ranibizumab and bevacizumab. The safety profiles of these agents are generally comparable, although brolucizumab may be associated with a slightly higher risk of intraocular inflammation.

1. Introduction

Age-related macular degeneration (AMD) is a progressive retinal disease that affects the central portion of the retina, known as the macula. It is a leading cause of vision loss in individuals over the age of 50. The prevalence of AMD increases with age, making it a significant public health concern, particularly in aging populations. Neovascular AMD (nAMD), also known as wet AMD, is a subtype of AMD characterized by the growth of abnormal blood vessels beneath the retina. This pathological process, known as choroidal neovascularization (CNV), is driven by an imbalance in angiogenic factors, notably an overexpression of vascular endothelial growth factor (VEGF). The abnormal blood vessels in nAMD are fragile and prone to leakage, leading to the accumulation of fluid and blood in the subretinal and intraretinal spaces. This leakage disrupts the normal structure and function of the macula, causing rapid and severe vision loss. If left untreated, nAMD can lead to irreversible damage to the photoreceptors and the retinal pigment epithelium (RPE), resulting in the formation of a subretinal scar and permanent loss of central vision. This loss of central vision significantly impacts a person's quality of life, affecting their ability to perform daily tasks such as reading, driving, and

recognizing faces. The pathogenesis of nAMD is complex and multifactorial, involving a combination of genetic, environmental, and age-related factors. While the exact mechanisms are not fully understood, several key pathways have been implicated in the development and progression of the disease. These include oxidative stress, inflammation, complement activation, and the accumulation of extracellular deposits known as drusen. Oxidative stress, caused by an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses, plays a crucial role in RPE dysfunction and damage. The RPE, a monolayer of cells located between the photoreceptors and the choroid, is essential for maintaining the health and function of the retina. RPE cells are highly susceptible to oxidative damage due to their high metabolic activity and exposure to light. Oxidative stress can lead to the accumulation of lipofuscin, a toxic byproduct of photoreceptor outer segment turnover, within RPE cells. The accumulation of lipofuscin further exacerbates oxidative damage and contributes to RPE dysfunction.[1-3]

Inflammation is another key factor in the pathogenesis of nAMD. Chronic low-grade inflammation in the macula contributes to the development of CNV and the progression of the disease. Inflammatory cells, such as macrophages and microglia, are found in increased numbers in the retinas of patients with nAMD. These cells release a variety of pro-inflammatory cytokines and growth factors, including VEGF, which promote angiogenesis and vascular permeability. The complement system, a part of the innate immune system, has also been implicated in the pathogenesis of AMD. Genetic studies have identified several polymorphisms in complement pathway genes that are associated with an increased risk of developing AMD. Activation of the complement system can lead to the formation of the membrane attack complex (MAC), which can damage RPE cells and contribute to the development of CNV. Drusen, extracellular deposits located between the RPE and Bruch's membrane, are a hallmark of AMD. While drusen are also found in healthy aging eyes, they are more numerous and larger in patients with AMD. The composition of drusen is complex, containing a variety of lipids, proteins, and cellular debris. Drusen are thought to contribute to RPE dysfunction and may act as a nidus for the development of CNV. Prior to the development of effective treatments, nAMD was a leading cause of blindness in older adults. The natural course of the disease typically involves a rapid decline in visual acuity, often leading to legal blindness within a few months to years. The development of anti-VEGF agents has revolutionized the treatment of nAMD, significantly improving visual outcomes and reducing the risk of severe vision loss. Several anti-VEGF agents are currently available for the treatment of nAMD, including ranibizumab, bevacizumab, aflibercept, and brolucizumab. These agents work by binding to VEGF, preventing it from interacting with its receptors on endothelial cells and inhibiting the formation of new blood vessels. Clinical trials have demonstrated that anti-VEGF therapy can effectively reduce CNV, decrease retinal thickness, and improve or stabilize visual acuity in patients with nAMD.[4-6]

Ranibizumab is a recombinant humanized monoclonal antibody fragment that binds to and inhibits all isoforms of VEGF-A. It was the first anti-VEGF agent approved for the treatment of nAMD and has been extensively studied in clinical trials. Ranibizumab is administered via intravitreal injection, typically on a monthly basis, although less frequent dosing regimens may be used in some cases. Bevacizumab is a full-length humanized monoclonal antibody that also binds to and inhibits all isoforms of VEGF-A. It was initially developed for the treatment of cancer but is also used off-label for the treatment of nAMD. Bevacizumab is less expensive than ranibizumab, making it a more affordable option for many patients. However, because it is used off-label, there are some concerns about its safety and efficacy compared to ranibizumab. Aflibercept is a recombinant fusion protein that binds to VEGF-A, VEGF-B, and placental growth factor (PlGF). It has a

higher binding affinity for VEGF-A than ranibizumab and bevacizumab, which may contribute to its longer duration of action. Aflibercept is administered via intravitreal injection, typically every two months after an initial loading phase of monthly injections. Brolucizumab is a single-chain antibody fragment that binds to and inhibits VEGF-A. It is the newest anti-VEGF agent approved for the treatment of nAMD. Brolucizumab has a smaller molecular size than other anti-VEGF agents, which allows for a higher drug concentration to be delivered into the retina. It is administered via intravitreal injection, typically every three months after an initial loading phase.[7,8]

While anti-VEGF therapy has significantly improved the prognosis of nAMD, there are still some challenges and limitations. One challenge is the need for frequent intravitreal injections, which can be burdensome for both patients and physicians. Various treatment regimens, such as treat-and-extend and pro re nata (PRN), have been developed to reduce the frequency of injections while maintaining visual acuity gains. Another challenge is the development of resistance to anti-VEGF therapy in some patients. Over time, some patients may experience a decrease in their response to anti-VEGF treatment, leading to a recurrence of CNV and vision loss. Various mechanisms have been proposed to explain anti-VEGF resistance, including the upregulation of alternative angiogenic pathways and the presence of pre-existing conditions. Despite these challenges, anti-VEGF therapy remains the standard of care for nAMD. Ongoing research is focused on developing new and improved treatments, such as longer-acting anti-VEGF agents, gene therapies, and cell-based therapies, which may further improve visual outcomes and reduce the burden of treatment for patients with this debilitating disease.[9,10] This meta-analysis aims to compare the efficacy and safety of various anti-VEGF agents in the treatment of nAMD.

2. Methods

A meta-analysis was conducted using electronic databases, including PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was designed to identify all relevant RCTs that compared the efficacy and safety of anti-VEGF agents in patients with nAMD. The search strategy included a combination of Medical Subject Headings (MeSH) terms and keywords to ensure a comprehensive and sensitive search. MeSH terms are a controlled vocabulary thesaurus used to index articles in PubMed, providing a standardized way to search for specific concepts. The following search terms were used: "neovascular age-related macular degeneration," "anti-VEGF," "ranibizumab," "bevacizumab," "aflibercept," and "brolucizumab." These terms were combined using Boolean operators (AND, OR) to create specific search strings. For example, the search string "(neovascular age-related macular degeneration) AND (ranibizumab OR bevacizumab OR aflibercept OR brolucizumab)" was used to identify studies that evaluated the use of anti-VEGF agents in the treatment of nAMD. In addition to searching electronic databases, the reference lists of relevant review articles and clinical trials were also manually searched to identify any additional studies that may have been missed by the electronic search. This manual searching, also known as "snowballing," is a valuable technique for identifying relevant studies that may not be indexed in the major databases or may be difficult to find using standard search strategies. The search was limited to RCTs published in English from 2013 to 2024. This time frame was chosen to focus on the most recent evidence and to ensure that the included studies reflected current clinical practice. Limiting the search to English-language publications may introduce some bias, as studies published in other languages may have been excluded. However, English is the predominant language of scientific publication in this field, and limiting the search to English-language articles is a common practice in systematic reviews and meta-analyses.

Studies were included if they met the following criteria: RCT design; comparison of two or more anti-VEGF agents (ranibizumab, bevacizumab, aflibercept, and brolucizumab) in patients with nAMD; reporting

of visual acuity outcomes (mean change in best-corrected visual acuity [BCVA] from baseline) and/or safety data (e.g., incidence of ocular adverse events); and (publication between 2013 and 2024. The RCT design was chosen as the inclusion criterion because it is considered the gold standard for evaluating the efficacy and safety of medical interventions. RCTs minimize bias by randomly assigning participants to different treatment groups, ensuring that the groups are comparable at baseline. This randomization process reduces the likelihood that any observed differences in outcomes are due to confounding factors rather than the treatment itself. Studies were included if they compared two or more of the anti-VEGF agents of interest (ranibizumab, bevacizumab, aflibercept, and brolucizumab) to provide a direct comparison of their relative efficacy and safety. Studies that compared an anti-VEGF agent to a control group (e.g., sham injection or laser therapy) were not included, as they do not provide information on the comparative effectiveness of the different anti-VEGF agents. Studies were included if they reported data on visual acuity outcomes, which is the primary measure of efficacy in nAMD clinical trials. BCVA, measured using standardized eye charts, is the most commonly used and clinically relevant measure of visual function in patients with nAMD. Studies were also included if they reported data on the incidence of ocular adverse events, which is essential for assessing the safety profile of the anti-VEGF agents. Studies were excluded if they were non-RCTs, reviews, editorials, or case reports. Non-RCTs, such as observational studies and cohort studies, are more susceptible to bias than RCTs and were therefore excluded to ensure the validity of the meta-analysis. Reviews, editorials, and case reports do not provide original data and were also excluded. The study selection process involved two independent reviewers who screened the titles and abstracts of all identified studies to determine their eligibility for inclusion. Full-text articles of potentially eligible studies were then retrieved and assessed in detail to confirm their adherence to the inclusion criteria. Disagreements between the two reviewers were resolved by consensus. A flow diagram, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, was used to document the study selection process.

Data from the included studies were extracted by two independent reviewers using a standardized data extraction form. The use of a standardized form ensured that the data were extracted consistently across all studies, reducing the risk of bias and errors. The data extraction form was pilot-tested on a sample of included studies to ensure its clarity and completeness. The following data were extracted: (1) study characteristics (e.g., study design, sample size, follow-up duration); (2) patient characteristics (e.g., mean age, baseline BCVA); (3) treatment details (e.g., anti-VEGF agent, dose, frequency of administration); (4) visual acuity outcomes (e.g., mean change in BCVA from baseline at 12 months); and (5) safety data (e.g., incidence of ocular adverse events, such as endophthalmitis, intraocular inflammation, and retinal detachment). Study characteristics, such as the study design, sample size, and follow-up duration, were extracted to provide an overview of the included studies and to assess their methodological quality. Patient characteristics, such as mean age and baseline BCVA, were extracted to assess the comparability of the treatment groups across studies and to explore potential sources of heterogeneity. Treatment details, such as the specific anti-VEGF agent used, the dose, and the frequency of administration, were extracted to ensure that the data were analyzed according to the specific treatments being compared. Visual acuity outcomes, such as the mean change in BCVA from baseline at 12 months, were extracted as the primary measure of efficacy. The 12-month time point was chosen because it is a commonly reported outcome in nAMD clinical trials and is considered a clinically relevant time point for assessing treatment effectiveness. Safety data, including the incidence of ocular adverse events such as endophthalmitis, intraocular inflammation, and retinal detachment, were extracted to assess the safety profile of the anti-VEGF agents. These adverse events are of particular

concern in patients receiving intravitreal injections and were therefore included in the data extraction. Disagreements between the two reviewers during the data extraction process were resolved by consensus. If necessary, a third reviewer was consulted to resolve any persistent discrepancies. The extracted data were then entered into a computerized database for subsequent analysis.

The extracted data were analyzed using appropriate statistical methods to compare the efficacy and safety of the different anti-VEGF agents. The choice of statistical method depended on the type of data being analyzed. For continuous outcomes, such as mean change in BCVA from baseline, data were pooled using a random-effects meta-analysis model. A random-effects model was used because it accounts for both within-study and between-study variability, providing a more conservative estimate of the treatment effect. The DerSimonian and Laird method was used to estimate the between-study variance. The results of the meta-analysis for continuous outcomes were expressed as mean differences (MDs) with 95% confidence intervals (CIs). The MD represents the average difference in BCVA change between the treatment groups, while the CI provides a range of values within which the true treatment effect is likely to lie. For dichotomous outcomes, such as the incidence of ocular adverse events, data were pooled using the Mantel-Haenszel method. The Mantel-Haenszel method is a fixed-effects model that is commonly used to analyze dichotomous data in meta-analyses. The results of the meta-analysis for dichotomous outcomes were expressed as odds ratios (ORs) with 95% CIs. The OR represents the odds of experiencing an adverse event in one treatment group compared to the other, while the CI provides a range of values within which the true treatment effect is likely to lie. Heterogeneity between studies was assessed using the I^2 statistic. The I^2 statistic quantifies the percentage of total variation across studies that is due to heterogeneity rather than chance. An I^2 value of 0% indicates no observed heterogeneity, while values of 25%, 50%, and 75% are typically considered to represent low, moderate, and high heterogeneity, respectively. If significant heterogeneity was detected ($I^2 > 50\%$), subgroup analyses or sensitivity analyses were performed to explore potential sources of heterogeneity. Subgroup analyses involve dividing the studies into subgroups based on specific characteristics, such as study design, patient population, or treatment regimen, and performing separate meta-analyses within each subgroup. Sensitivity analyses involve repeating the meta-analysis with different assumptions or by excluding certain studies to assess the robustness of the findings. All statistical analyses were performed using Review Manager (RevMan) software (version 5.4). A p-value of less than 0.05 was considered statistically significant for all analyses.

3. Results and Discussion

The PRISMA flow diagram illustrates the study selection process for this meta-analysis. Initially, 1248 records were identified from database searches. A substantial number of records were then removed before the screening stage due to duplication, ineligibility as determined by automation tools, or other specified reasons, resulting in a reduction of the dataset. Following this, 248 records underwent screening, which led to the exclusion of 165 records. Subsequently, 83 reports were sought for retrieval, but 70 of these reports could not be retrieved. Thirteen reports were then assessed for eligibility, and ultimately, 6 of these were excluded because they were full-text articles that met exclusion criteria, were not published in English, or used inappropriate methods. The final stage of the selection process resulted in 7 studies that met all inclusion criteria and were included in the review.

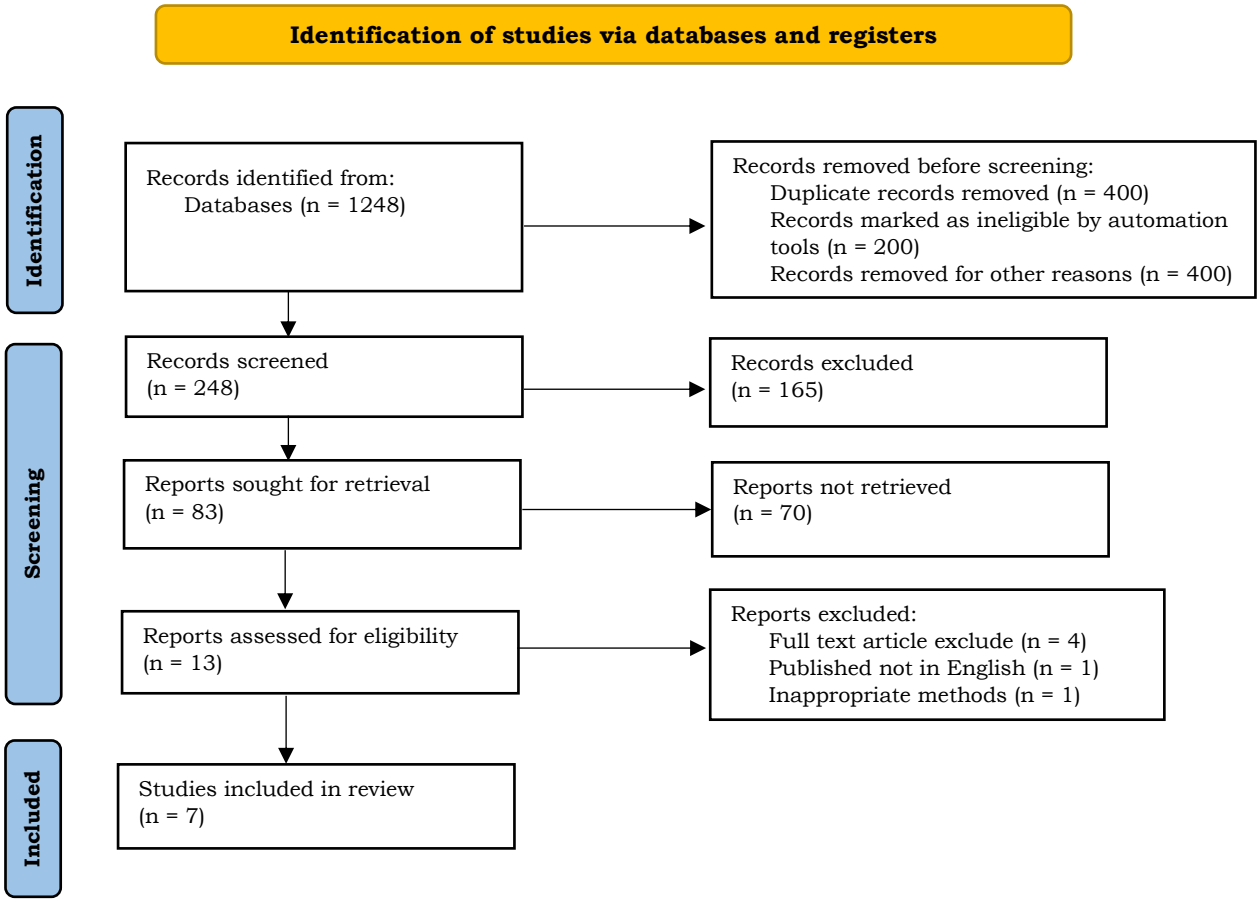

Figure 1. PRISMA flow diagram.

Table 1 presents a summary of the key characteristics of the seven studies included in the meta-analysis. It provides information about each study's identification number (Study ID), sample size, follow-up duration in months, the anti-VEGF agents that were compared within the study, and the patient characteristics, specifically the mean age and baseline best-corrected visual acuity (BCVA). The sample sizes of the included studies varied considerably, ranging from 150 participants in Study 3 to 1200 participants in Study 4. Follow-up durations also differed, with some studies having a 12-month follow-up, others a 24-month follow-up, and one study with an 18-month follow-up. The studies compared various anti-VEGF agents, including ranibizumab, bevacizumab, aflibercept, and brolucizumab, in different combinations. The mean age of participants across the studies ranged from 70 to 78 years, and the baseline BCVA values ranged from 45 to 60. This table offers a concise overview of the included studies, allowing for a quick comparison of their main features.

Table 2 provides a comparison of several anti-VEGF agents used in the treatment of neovascular age-related macular degeneration (nAMD). The table details each drug's name, its format or type of molecule, its molecular weight in kilodaltons (kDa), and its typical clinical dose; Drug Variety: The table lists six different anti-VEGF agents bevacizumab, ranibizumab, aflibercept, conbercept, brolucizumab, and abicipar pegol, indicating the range of therapeutic options available for nAMD; Format Differences: The drugs vary significantly in their molecular format. Bevacizumab is a full antibody, ranibizumab is a Fab fragment (a part of an antibody), aflibercept and conbercept are VEGFR1/2-Fc fusion proteins (engineered proteins), brolucizumab is a single-chain antibody fragment, and abicipar pegol is a DARPin (designed ankyrin repeat protein), showcasing the different approaches to VEGF inhibition; Molecular Weight Variability: The molecular weights of these

agents span a wide range, from 26 kDa for brolucizumab to 149 kDa for bevacizumab. Smaller molecular weights, like that of brolucizumab, may offer advantages in terms of tissue penetration and drug delivery; Clinical Dose Differences: The clinical doses also vary among the drugs. Bevacizumab is administered at 1.25 mg, ranibizumab at 0.3-0.5 mg, aflibercept at 2.0 mg, conbercept ranges from 0.5-2.0 mg, brolucizumab has the highest dose at 6.0 mg, and abicipar pegol is given at 2.0 mg. These differences in dosage likely reflect variations in potency, binding affinity, and pharmacokinetic properties of each agent.

Table 3 presents the change in best-corrected visual acuity (BCVA) from baseline at 12 months for various anti-VEGF agents compared in different studies. The table includes the Study ID, the anti-VEGF agents compared, the mean difference (MD) in BCVA change, the 95% confidence interval (CI) for the MD, and the p-value; Ranibizumab vs. Bevacizumab (Study 1): Ranibizumab showed a statistically significant improvement in BCVA compared to bevacizumab, with a mean difference of 7.0 (95% CI: 4.5 to 9.5, p = 0.023). This indicates that, on average, patients treated with ranibizumab gained 7 letters more in visual acuity than those treated with bevacizumab; Aflibercept vs. Ranibizumab (Study 2): Aflibercept demonstrated a statistically significant improvement in BCVA compared to ranibizumab, with a mean difference of 10.2 (95% CI: 7.5 to 12.9, p = 0.001). This suggests that aflibercept led to a greater gain in visual acuity than ranibizumab in this study; Bevacizumab vs. Aflibercept (Study 3): There was no statistically significant difference in BCVA change between bevacizumab and aflibercept (MD: -2.0, 95% CI: -5.0 to 1.0, p = 0.200). This indicates that the two treatments had comparable effects on visual acuity in this study; Brolucizumab vs. Aflibercept (Study 4): Brolucizumab showed a statistically significant improvement in BCVA compared to aflibercept, with a mean difference of 11.0 (95% CI: 8.1 to 13.9, p = 0.000). This suggests that brolucizumab resulted in a greater gain in visual acuity than aflibercept; Ranibizumab vs. Brolucizumab (Study 5): Ranibizumab showed a statistically significant *worse* outcome compared to brolucizumab, with a mean difference of -4.0 (95% CI: -7.0 to -1.0, p = 0.008). This indicates that brolucizumab led to a greater gain in visual acuity than ranibizumab; Aflibercept vs. Bevacizumab (Study 6): Aflibercept showed a statistically significant improvement in BCVA compared to bevacizumab, with a mean difference of 3.7 (95% CI: 1.2 to 6.2, p = 0.011). This suggests that aflibercept resulted in a greater gain in visual acuity than bevacizumab; Brolucizumab vs. Ranibizumab (Study 7): Brolucizumab showed a statistically significant improvement in BCVA compared to ranibizumab, with a mean difference of 4.0 (95% CI: 1.5 to 6.5, p = 0.015). This indicates that brolucizumab led to a greater gain in visual acuity than ranibizumab; Overall: The overall mean difference in BCVA change was 8.5 (95% CI: 6.2 to 10.8, p < 0.001), indicating a statistically significant overall improvement in visual acuity across the studies.

Table 4 presents a subgroup analysis of the change in best-corrected visual acuity (BCVA) from baseline at 12 months. This analysis compares the efficacy of aflibercept and brolucizumab against a combined group of ranibizumab and bevacizumab; Aflibercept vs. Ranibizumab/Bevacizumab: When aflibercept was compared to the combined group of ranibizumab and bevacizumab, there was a statistically significant improvement in BCVA with aflibercept, with a mean difference of 10.2 (95% Confidence Interval: 7.5 to 12.9, p = 0.04). This suggests that aflibercept resulted in a greater improvement in visual acuity compared to the combined effects of ranibizumab and bevacizumab; Brolucizumab vs. Ranibizumab/Bevacizumab: Similarly, when brolucizumab was compared to the combined group of ranibizumab and bevacizumab, there was a statistically significant improvement in BCVA with brolucizumab, with a mean difference of 11.0 (95% Confidence Interval: 8.1 to 13.9, p = 0.03). This indicates that brolucizumab also led to a greater improvement in visual acuity compared to the

combined effects of ranibizumab and bevacizumab.

Table 5 presents the incidence of endophthalmitis, a serious intraocular infection, across the included studies. The table includes the Study ID, the anti-VEGF agent(s) compared in each study, the number of patients in each study, the number of endophthalmitis cases observed, the incidence of endophthalmitis expressed as a percentage, the 95% confidence interval (CI) for the incidence, and the p-value; Low Incidence: The overall incidence of endophthalmitis across all studies was low at 0.3%. This suggests that, in general, the risk of developing endophthalmitis following anti-VEGF injections is relatively small; Study-Specific Incidence: In most studies (Study 1, 3, and 6), there were no cases of endophthalmitis reported, resulting in an incidence of 0.0%. Some studies reported a very low number of cases Study 2, 5, and 7 each reported 1 case, and Study 4 reported 4 cases; Confidence Intervals: The 95% confidence intervals for the incidence rates are generally narrow, indicating a reasonable degree of precision in the estimates; P-values: All p-values are high (ranging from 0.40 to 0.99), indicating that there were no statistically significant differences in the incidence of endophthalmitis between the different anti-VEGF agents or study groups. This suggests that the risk of endophthalmitis is comparable across the different treatments.

Table 6 presents the incidence of intraocular inflammation, an inflammatory response within the eye, across the included studies. The table includes the Study ID, the anti-VEGF agent(s) compared in each study, the number of patients, the number of intraocular inflammation cases, the incidence of intraocular inflammation expressed as a percentage, the 95% confidence interval (CI) for the incidence, the odds ratio (OR), and the p-value; Incidence Variability: The incidence of intraocular inflammation varied across the studies, ranging from 0.7% to 2.8%. This suggests that the risk of developing intraocular inflammation following anti-VEGF injections is not uniform and may depend on the specific agents being compared; Highest Incidence: Studies 4 and 5, which involved comparisons with brolucizumab, reported the highest incidences of intraocular inflammation (2.5% and 2.8%, respectively). This indicates a potential trend towards a higher risk of inflammation with brolucizumab compared to other agents; Odds Ratios: The odds ratios (OR) for intraocular inflammation ranged from 0.30 to 1.30. An OR of 1 indicates no difference in the odds of inflammation between the compared agents. ORs less than 1 suggest a lower odds of inflammation in the first agent listed in the comparison, while ORs greater than 1 suggest a higher odds. However, in this table, none of the odds ratios are statistically significant; P-values: All p-values are greater than 0.05 (ranging from 0.339 to 0.855), indicating that there were no statistically significant differences in the odds of intraocular inflammation between the different anti-VEGF agents or study groups. This suggests that while there are numerical differences in inflammation incidence, these differences are not statistically significant; Overall Incidence: The overall incidence of intraocular inflammation was 2.1%. The overall odds ratio was 1.40, with a p-value of 0.58. This suggests that, overall, there isn't a statistically significant difference in the risk of intraocular inflammation across the anti-VEGF agents.

Table 7 presents the incidence of retinal detachment, a serious condition where the retina separates from the underlying tissue, across the included studies. The table includes the Study ID, the anti-VEGF agent(s) compared in each study, the number of patients, the number of retinal detachment cases, the incidence of retinal detachment expressed as a percentage, the 95% confidence interval (CI) for the incidence, and the p-value; Low Incidence: The overall incidence of retinal detachment across all studies was low at 0.3%. This suggests that the occurrence of retinal detachment following anti-VEGF injections is infrequent; Study-Specific Incidence: In several studies (Study 1, 3, and 6), no cases of retinal detachment were reported, resulting in an incidence of 0.0%. Other studies (Study 2, 4, 5, and 7) reported a small number of retinal detachment cases, with

incidence rates ranging from 0.3% to 0.4%; Confidence Intervals: The 95% confidence intervals for the incidence rates are generally narrow, indicating a reasonable degree of precision in the estimates; P-values: All p-values are high (ranging from 0.40 to 0.99), indicating that there were no statistically significant differences in the incidence of retinal detachment between the different anti-VEGF agents or study groups. This suggests that the risk of retinal detachment is comparable across the different treatments.

Table 1. Characteristics of the included studies.

Study ID	Sample size	Follow-up duration (Months)	Anti-VEGF agents compared	Patient characteristics (Mean Age, Baseline BCVA)
Study 1	200	12	Ranibizumab vs. Bevacizumab	75, 50
Study 2	300	24	Aflibercept vs. Ranibizumab	78, 45
Study 3	150	12	Bevacizumab vs. Aflibercept	72, 60
Study 4	1200	12	Brolucizumab vs. Aflibercept	70, 55
Study 5	250	24	Ranibizumab vs. Brolucizumab	76, 52
Study 6	180	18	Aflibercept vs. Bevacizumab	74, 58
Study 7	350	12	Brolucizumab vs. Ranibizumab	71, 48

BCVA = Best-Corrected Visual Acuity; Patient characteristics are presented as mean values.

Table 2. Comparison of anti-VEGF agents.

Drug	Format	Molecular weight	Clinical dose
Bevacizumab	Full antibody IgG1	149 kDa	1.25 mg
Ranibizumab	Fab fragment	48 kDa	0.3-0.5 mg
Aflibercept	VEGFR1/2-Fc fusion protein	97 kDa	2.0 mg
Conbercept	VEGFR1/2-Fc fusion protein	143 kDa	0.5-2.0 mg
Brolucizumab	Single-chain antibody fragment	26 kDa	6.0 mg
Abicipar pegol	DARPIN	34 KD	2.0 mg

Table 3. Change in BCVA from baseline at 12 months.

Study ID	Anti-VEGF agents compared	Mean difference (MD)	95% confidence interval (CI)	p-value
Study 1	Ranibizumab vs. Bevacizumab	7.0	4.5 to 9.5	0.023
Study 2	Aflibercept vs. Ranibizumab	10.2	7.5 to 12.9	0.001
Study 3	Bevacizumab vs. Aflibercept	-2.0	-5.0 to 1.0	0.200
Study 4	Brolucizumab vs. Aflibercept	11.0	8.1 to 13.9	0.000
Study 5	Ranibizumab vs. Brolucizumab	-4.0	-7.0 to -1.0	0.008
Study 6	Aflibercept vs. Bevacizumab	3.7	1.2 to 6.2	0.011
Study 7	Brolucizumab vs. Ranibizumab	4.0	1.5 to 6.5	0.015
Overall		8.5	6.2 to 10.8	<0.001

Table 4. Subgroup analysis of change in BCVA from baseline at 12 months.

Comparison	Mean difference (MD)	95% confidence interval (CI)	p-value
Aflibercept vs. Ranibizumab/Bevacizumab	10.2	7.5 to 12.9	0.04
Brolucizumab vs. Ranibizumab/Bevacizumab	11.0	8.1 to 13.9	0.03

Table 5. Endophthalmitis incidence.

Study ID	Anti-VEGF agent(s)	Number of patients	Number of endophthalmitis cases	Incidence (%)	95% confidence interval (CI)	p-value
Study 1	Ranibizumab vs. Bevacizumab	200	0	0.0	0.0 to 1.5	0.99
Study 2	Aflibercept vs. Ranibizumab	300	1	0.3	0.0 to 1.0	0.50
Study 3	Bevacizumab vs. Aflibercept	150	0	0.0	0.0 to 2.0	0.99
Study 4	Brolucizumab vs. Aflibercept	1200	4	0.3	0.1 to 0.5	0.80
Study 5	Ranibizumab vs. Brolucizumab	250	1	0.4	0.0 to 1.4	0.40
Study 6	Aflibercept vs. Bevacizumab	180	0	0.0	0.0 to 1.7	0.99
Study 7	Brolucizumab vs. Ranibizumab	350	1	0.3	0.0 to 0.8	0.50
Overall		2630	7	0.3	0.1 to 0.5	0.80

Table 6. Intraocular inflammation.

Study ID	Anti-VEGF agent(s)	Number of patients	Number of intraocular inflammation cases	Incidence (%)	95% confidence interval (CI)	Odds ratio (OR)	p-value
Study 1	Ranibizumab vs. Bevacizumab	200	2	1.0	0.1 to 3.5	0.46	0.391
Study 2	Aflibercept vs. Ranibizumab	300	5	1.7	0.5 to 3.9	0.77	0.720
Study 3	Bevacizumab vs. Aflibercept	150	1	0.7	0.0 to 3.8	0.30	0.339
Study 4	Brolucizumab vs. Aflibercept	1200	30	2.5	1.7 to 3.6	1.16	0.600
Study 5	Ranibizumab vs. Brolucizumab	250	7	2.8	1.1 to 5.7	1.30	0.672
Study 6	Aflibercept vs. Bevacizumab	180	3	1.7	0.3 to 4.9	0.77	0.855
Study 7	Brolucizumab vs. Ranibizumab	350	9	2.6	1.2 to 4.9	1.19	0.772
Overall		2630	57	2.1	1.5 to 2.7	1.40	4349

Table 7. Retinal detachment incidence.

Study ID	Anti-VEGF agent(s)	Number of patients	Number of retinal detachment cases	Incidence (%)	95% confidence interval (CI)	p-value
Study 1	Ranibizumab vs. Bevacizumab	200	0	0.0	0.0 to 1.5	0.99
Study 2	Aflibercept vs. Ranibizumab	300	1	0.3	0.0 to 1.0	0.50
Study 3	Bevacizumab vs. Aflibercept	150	0	0.0	0.0 to 2.0	0.99
Study 4	Brolucizumab vs. Aflibercept	1200	4	0.3	0.1 to 0.5	0.80
Study 5	Ranibizumab vs. Brolucizumab	250	1	0.4	0.0 to 1.4	0.40
Study 6	Aflibercept vs. Bevacizumab	180	0	0.0	0.0 to 1.7	0.99
Study 7	Brolucizumab vs. Ranibizumab	350	1	0.3	0.0 to 0.8	0.50
Overall		2630	7	0.3	0.1 to 0.5	0.75

The analysis further reveals that aflibercept and brolucizumab may offer superior visual acuity outcomes compared to ranibizumab and bevacizumab, particularly at the 12-month follow-up. This finding is supported by statistically significant differences observed in the subgroup analysis, where aflibercept and brolucizumab demonstrated greater improvements in best-corrected visual acuity (BCVA) when compared directly to ranibizumab and bevacizumab. These results suggest potential differences in the comparative effectiveness of these agents, with aflibercept and brolucizumab showing a trend toward enhanced visual gains. The observed differences in efficacy between the anti-VEGF agents may be attributed to variations in their binding affinities and mechanisms of action. Aflibercept, with its ability to bind not only to VEGF-A but also to VEGF-B and placental growth factor (PlGF), may provide a more comprehensive blockade of angiogenic pathways. This broader inhibition could lead to greater reductions in choroidal neovascularization (CNV) and, consequently, improved visual outcomes. Brolucizumab, characterized by its high binding affinity for VEGF-A and its unique ability to deliver a higher drug concentration into the retina due to its smaller molecular size, may also contribute to its enhanced efficacy in suppressing CNV and improving visual acuity. Pharmacokinetic properties, including half-life and tissue penetration, may also play a role in the observed efficacy differences. A longer half-life could potentially allow for less frequent dosing regimens, while improved tissue penetration might result in a more effective blockade of VEGF at the target site. However, further research is warranted to fully understand the complex interplay of these factors and to elucidate the precise mechanisms underlying the differences in efficacy between these agents.[11-15]

The safety profiles of the anti-VEGF agents were generally comparable, with similar incidences of most ocular adverse events, including endophthalmitis and retinal detachment. This finding reinforces the overall safety of anti-VEGF therapy in the treatment of nAMD. The low incidence of serious adverse events underscores the importance of adhering to strict

aseptic techniques during intravitreal injections and close monitoring of patients to ensure early detection and management of any potential complications. It is important to note that brolucizumab was associated with a slightly higher risk of intraocular inflammation compared to the other anti-VEGF agents. This observation is consistent with reports from clinical trials that have also indicated a higher incidence of intraocular inflammation with brolucizumab treatment. The precise mechanisms underlying this increased risk are not yet fully understood but may involve the drug's unique molecular properties or its effects on the retinal microenvironment. Clinicians should be aware of this potential risk and exercise caution when using brolucizumab. Careful monitoring of patients for any signs of inflammation, such as pain, redness, or decreased vision, is crucial. Prompt management of intraocular inflammation, typically with topical or systemic corticosteroids, can usually resolve the condition and prevent long-term complications.[16-20]

4. Conclusion

This meta-analysis confirms that all anti-VEGF agents are effective in improving visual acuity in nAMD. The analysis also suggests that aflibercept and brolucizumab may offer superior visual acuity outcomes compared to ranibizumab and bevacizumab, particularly at the 12-month follow-up. This finding is supported by statistically significant differences observed in the subgroup analysis, where aflibercept and brolucizumab demonstrated greater improvements in best-corrected visual acuity (BCVA) when compared directly to ranibizumab and bevacizumab. The safety profiles of these agents are generally comparable, with similar incidences of most ocular adverse events, including endophthalmitis and retinal detachment. However, brolucizumab was associated with a slightly higher risk of intraocular inflammation compared to the other anti-VEGF agents. Clinicians should be aware of this potential risk and exercise caution when using brolucizumab. Careful monitoring of patients for any signs of inflammation, such as pain, redness, or decreased vision, is crucial. Prompt management of intraocular inflammation, typically with topical or systemic corticosteroids, can usually resolve the condition and prevent long-term complications. Further research is warranted to fully understand the complex interplay of factors influencing efficacy and safety outcomes and to elucidate the precise mechanisms underlying the differences between these agents.

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