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Long-Term Outcomes of Anti-VEGF Therapy in Neovascular Age-Related Macular Degeneration: A Systematic Review

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ABSTRACT

Objectives: To systematically assess the long-term outcomes of anti-vascular endothelial growth factors (anti-VEGF) therapy in patients with neovascular age-related macular degeneration (nAMD).

Methods: A thorough search across four databases identified 563 relevant publications. After removing duplicates using Rayyan QCRI and screening for relevance, 322 full-text articles were reviewed, with 7 studies ultimately meeting the criteria for inclusion.

Results: We included seven studies with a total of 2013 nAMD patients and less than half of them were males 850 (42.2%). Long-term anti-VEGF therapy in nAMD demonstrates sustained efficacy, though several key outcomes have emerged. First, retinal perfusion changes were inconsistent, with no clear correlation between injection frequency and peripapillary perfusion. Despite long-term therapy, some patients experienced persistent macular neovascularization. Additionally, the gradual development of retinal atrophy was a common outcome after 3-5 years, contributing to a modest decline in visual function over time. Retinal vascular density, particularly in the superficial plexus, also decreased with prolonged treatment. Overall, while anti-VEGF therapy is well-tolerated and effective initially, these long-term structural changes may limit its sustained visual benefits.

Conclusion: Anti-VEGF therapy has significantly improved the prognosis for patients with nAMD, offering stabilization or improvement in vision and reducing the risk of severe visual loss. However, long-term outcomes highlight important challenges, such as the gradual development of retinal atrophy and the persistence of macular neovascularization (MNV) in some patients.

Keywords: Neovascular age-related macular degeneration; Anti-VEGF therapy; Long-term outcomes; Systematic review.

INTRODUCTION

The quality of life of those who are impacted by age-related macular degeneration (AMD), the primary cause of permanent vision loss and blindness in the developed world, as well as healthcare systems, is significantly impacted [1,2]. AMD accounted for 5% of all blindness cases reported globally in 2010 [3], and the total cost of treating AMD-related visual impairment exceeded $343 billion [4]. Since aging is the biggest risk factor for AMD, as the global population ages, it is anticipated that both the disease's prevalence and the related socioeconomic burden would rise sharply. AMD is predicted to affect around 196 million people globally by the end of 2020, rising to 288 million by 2040 [5].

The majority of blindness cases are caused by nAMD, which is the most prevalent late stage of AMD. Although it only makes up 10% of AMD cases, nAMD causes 80–90% of legally caused blindness [6]. Anti-VEGFs are treatments that target vascular endothelial growth factors (VEGFs), important angiogenesis mediators, to reduce or prevent aberrant vessel growth. Many work by attaching themselves to VEGFs and blocking their receptors from interacting, which inhibits VEGF activity [7, 8]. For many patients with nAMD, the use of anti-VEGFs has resulted in a notable improvement in visual results [9].

Brolucizumab, ranibizumab, and aflibercept are the three first-line anti-VEGFs used to treat AMD. The recombinant protein aflibercept (Eylea) binds to several isoforms of human VEGF-A, VEGF-B, and placental growth factor, functioning as a decoy receptor [10]. For the first three months, it is advised and authorized to take it once every four weeks (Q4), after which it should be taken once every eight weeks (Q8). After a year of effective treatment, some patients may switch to quarterly medication (once every 12 weeks [Q12]), while others may still require Q4 dosing [11].

nAMD is a leading cause of vision loss in the elderly, significantly impacting the quality of life. Anti-VEGF therapy has been a groundbreaking treatment, effectively controlling disease progression and preserving vision in the short to medium term. However, long-term outcomes of this therapy remain a subject of ongoing study. Understanding these outcomes is essential to evaluate the therapy's sustained effectiveness, potential side effects, and the overall impact on patient health and well-being. Despite its widespread use, gaps in knowledge about long-term visual acuity, treatment adherence, and complications like macular atrophy and fibrosis necessitate further investigation [6, 7].

The objective of this research is to systematically assess the long-term outcomes of anti-VEGF therapy in patients with nAMD. This study aims to evaluate the sustained efficacy in maintaining or improving vision, the incidence of adverse events, and the development of treatment-related complications over time. Additionally, the research explores patient compliance with long-term therapy regimens and the overall quality of life, aiming to provide a comprehensive understanding of the benefits and challenges associated with prolonged anti-VEGF use.

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METHODS

Search strategy

The systematic review followed the PRISMA and GATHER criteria. A thorough search was conducted to find relevant studies describing anti-VEGF for nAMD. The reviewers searched four electronic databases: PubMed, Web of Science, and SCOPUS. Studies published up until September 2024 were included. We uploaded all of the titles and abstracts found through electronic searches into Rayyan and omitted any duplicates. All the texts of all studies that satisfied the inclusion criteria based on title or abstract were then collected for comprehensive inspection. Two reviewers separately evaluated the appropriateness of the extracted papers and addressed any inconsistencies via discussion.

Ethical approval

Teaching Hospital, Sohag, of Medicine's Ethics Committee gave its approval to the project [No.: HSO00008-11/9/2024]. Every step of the inquiry was conducted in accordance with the Helsinki Declaration.

Study population—selection

The PICO (Population, Intervention, Comparison, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: Patients diagnosed nAMD, (ii) Intervention: Anti-VEGF, (iii) Comparator: Other treatments approaches, (iv) Outcome: effectiveness and long-term outcomes. Only primary investigations studying the administration of anti-VEGF to nAMD were included.

Data extraction

Two unbiased reviewers retrieved data from studies that met the inclusion criteria in a consistent and established format. The following information was retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Participants' number, (v) Age, (vi) Gender, (vii) Follow-up duration (in months) (viii) Key findings and long-term outcomes.

Quality review

We utilized the ROBINS-I technique to evaluate the risk of bias because it allows for extensive assessment of confounding, which is significant because bias owing to omitted variables is common in studies in this field. The ROBINS-I tool is intended to evaluate non-randomized investigations and can be applied to cohort designs in which participants exposed to various staffing levels are monitored over time. Two reviewers separately assessed the risk of bias for each paper, and disagreements were resolved through group discussion [12].

RESULTS

The specified search strategy yielded 563 publications. After removing duplicates (n =241), 322 trials were evaluated based on title and abstract. Of these, 242 failed to satisfy eligibility criteria, leaving just 80 full-text articles for comprehensive review. Two records were identified through citation search and only one was accepted into our review. A total of 7 satisfied the requirements for eligibility with evidence synthesis for analysis, including 4 retrospective cohorts [15-17,19], 2 cross-sectional studies [14,18] and one prospective cohort [20] **(Figure 1)**.

Sociodemographic and clinical outcomes

We included seven studies with a total of 2013 nAMD patients and less than half of them were males 850 (42.2%). Two studies were implemented in Switzerland [14,16], two in Germany [15,18], one in the UK [17], one in Finland [19], and one in Turkey [20]. The follow-up duration in this study ranged from 1 year to 14 years.

Long-term anti-VEGF therapy is generally considered safe and well-tolerated. Large cohort studies have confirmed that regular injections over several years do not lead to significant systemic adverse effects. However, there are concerns about local complications, such as intraocular pressure changes and rare cases of endophthalmitis, but these are typically manageable with appropriate clinical care [14-20].

Impact on Retina

Studies examining retinal perfusion in patients receiving long-term anti-VEGF therapy have shown mixed results. In particular, there was no consistent correlation between the frequency of anti-VEGF injections and peripapillary perfusion. Some studies noted altered perfusion density in nAMD patients compared to healthy controls, suggesting that the disease itself or the treatment could be influencing macular perfusion [14,15]. Long-term anti-VEGF therapy also appears to impact retinal vascular structure. Several studies have reported reduced vascular density, especially in the superficial retinal plexus, after prolonged therapy. This reduction in vascular density may contribute to retinal atrophy and visual decline [18].

Macular Neovascularization

Despite regular anti-VEGF therapy, some patients continue to exhibit macular neovascularization. The persistence of hyperpermeability and fluid exudation highlights a potential limitation of anti-VEGF treatment in fully controlling disease progression in certain cases [16].

Visual Function

Visual acuity outcomes in long-term anti-VEGF therapy patients show a modest decline over time. While many patients maintain improved or stabilized vision for the first few years of treatment, studies indicate a gradual decrease in visual function after extended therapy, particularly after five years. This visual decline is often attributed to the development of retinal atrophy or other structural changes in the retina, rather than a failure of the treatment to control neovascularization [17,19].

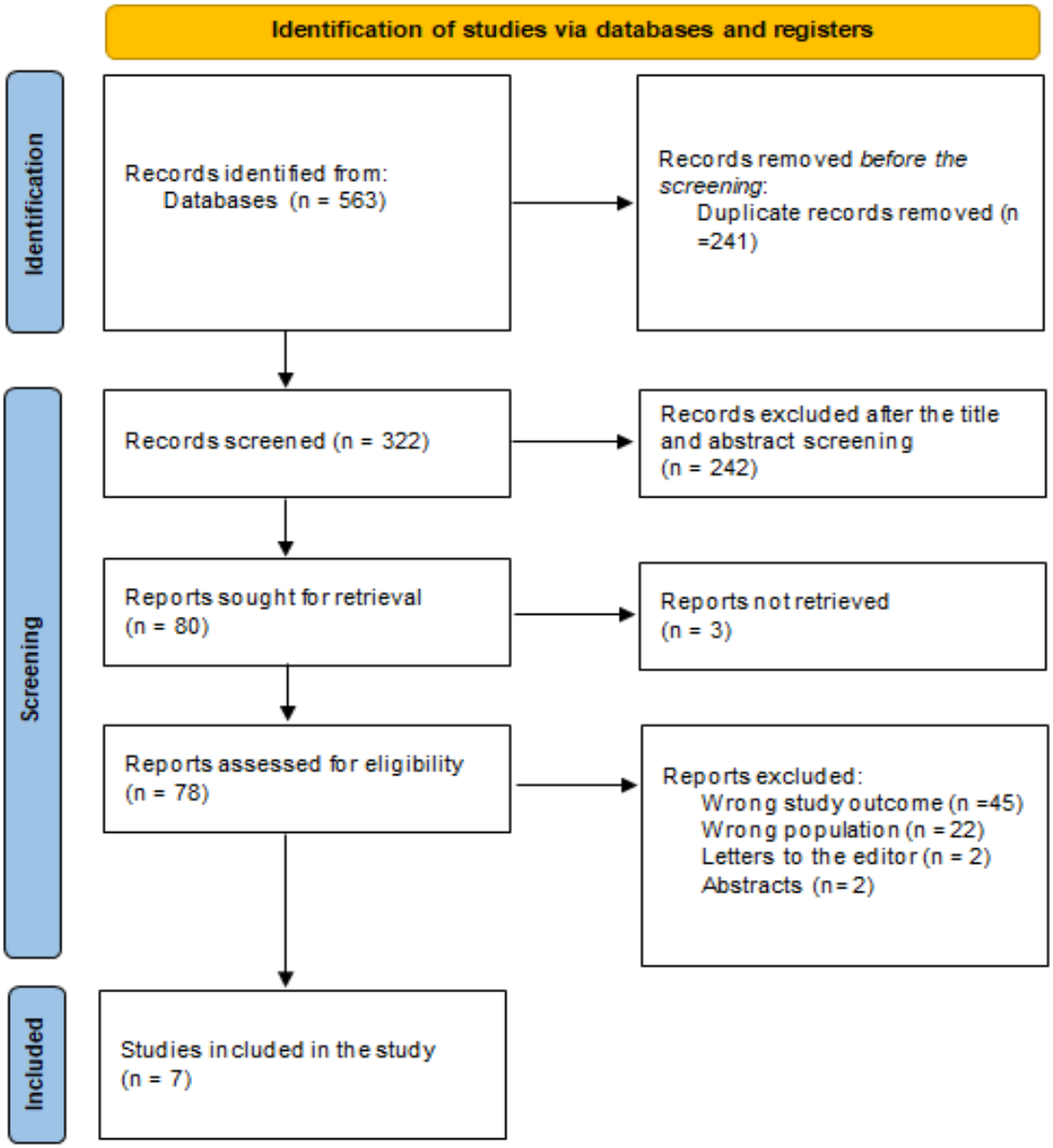

Figure (1): PRISMA flowchart [13].

Table (1): Outcome measures of the included studies

Study ID	Country	Study design	Sociodemographic	Follow-up (years)	Key findings
Türksever *et al.* 2023 [14]	Cross-sectional	Switzerland	N=21 Mean age: 77.9 Males: 12 (57.1%)	NM	Peripapillary perfusion characteristics did not correlate with the frequency of anti-VEGF medication in nAMD or post-operative IOP; nevertheless, patients with nAMD treated with anti-VEGF showed somewhat changed peripapillary perfusion in comparison to healthy controls. An impact of anti-VEGF medication or a feature of nAMD may be the lower macular perfusion density of the inner retina in nAMD patients compared to healthy controls.
Pauleikhoff *et al.* 2023 [15]	Retrospective cohort	Germany	N=94 Mean age: 75.9 Males: 31 (33%)	1 to 14	They noticed continued MNV proliferation in spite of frequent long-term anti-VEGF medication. This supports the idea that, if hyperpermeability and fluid exudation are managed, the creation of MNV may be a physiological repair mechanism to maintain RPE and photoreceptor function.
Munk *et al.*, 2016 [16]	Retrospective cohort	Switzerland	N=47 Mean age: 77 Males: 16 (34%)	4-8.5	Most individuals who receive long-term anti-VEGF therapy get retinal atrophy.
Corazza *et al.* 2021 [17]	Retrospective cohort	UK	N=780 Mean age: 85.5 Males: 353 (45.3%)	5	After the third year of follow-up, they discovered a modest decline in visual function despite long-term therapy.
Resch *et al.* 2022 [18]	Cross-sectional	Germany	N=42 Mean age: 74.8 Males: 22 (52.4%)	4	Compared to the deep retinal plexus, the superficial retinal plexus's vascular density is reduced more by long-term anti-VEGF therapy.
Adrean *et al.* 2018 [19]	Retrospective cohort	Finland	N=996 Mean age: 82.9 Males: 416 (41.8%)	6.4	For nAMD, regular, long-term anti-VEGF therapy is safe, effective, and can preserve or enhance visual results.
Inan *et al.* 2019 [20]	Prospective cohort	Turkey	N=33 Mean age: 72 Males: 18 (54.5%)	1	After receiving injections of ranibizumab for n-AMD for a year, notable alterations were noted in the thickness of the inner retinal layers. At month 12, the notable reduction in retinal pigment epithelium thickness that had been limited to the first several months vanished.

Table (2): Risk of bias assessment using ROBINS-I

Study ID	Bias due to confounding	Bias in the selection of participants into	Bias in the classification of interventions	Bias due to deviations from the intended interval	Bias due to missing data	Bias in the measurement of outcomes	Bias in the selection of reported result	Overall bias
Türksever *et al.* 2023 [14]	Low	Low	Low	Low	Low	Mod	Low	Low
Pauleikhoff *et al.* 2023 [15]	Low	Low	Mod	Low	Low	Low	Mod	Low
Munk *et al.* 2016 [16]	Mod	Low	Mod	Mod	Low	Mod	Mod	Moderate
Corazza *et al.* 2021 [17]	Mod	Mod	Low	Low	Low	Mod	Low	Moderate
Resch *et al.* 2022 [18]	Mod	Mod	Low	Low	Low	Low	Mod	Moderate
Adrean *et al.* 2018 [19]	Mod	Low	Low	Low	Mod	Mod	Low	Moderate
Inan *et al.* 2019 [20]	Crit	Low	Low	Crit	Low	Mod	Low	Critical

DISCUSSION

Although anti-VEGF therapy for nAMD has been utilized in clinical settings for over ten years, little is known about the advantages it offers patients and how it affects society as a whole. The objective of this research is to systematically assess the long-term outcomes of anti-VEGF therapy in patients with nAMD. This review demonstrated that long-term anti-VEGF therapy is generally considered safe and well-tolerated. Large cohort studies have confirmed that regular injections over several years do not lead to significant systemic adverse effects [14-20]. **Finger *et al.*** [21] reported that the number of nAMD patients undergoing treatment increased dramatically with the advent of anti-VEGF treatments, necessitating a rise in the resources allotted to nAMD therapy by healthcare systems. A substantial decrease in the prevalence of nAMD-related blindness, which is expensive for healthcare systems, can be clearly linked to the advent of anti-VEGF treatment.

This review stated that studies on retinal perfusion in patients undergoing long-term anti-VEGF therapy have shown varied results. There is no consistent relationship between injection frequency and peripapillary perfusion. Some findings suggest changes in perfusion density in nAMD patients, potentially influenced by the disease or the treatment itself. Additionally, prolonged anti-VEGF therapy has been associated with reduced vascular density, particularly in the superficial retinal plexus, which may contribute to retinal atrophy and subsequent visual decline [14,15,18]. This observation aligns with earlier research that also reported inconsistent changes in retinal perfusion after anti-VEGF treatment, possibly due to individual variations in disease progression and retinal vascular health reported reduction in vascular density, particularly in the superficial retinal plexus, after prolonged anti-VEGF therapy echoes findings from other studies that have explored the long-term structural changes associated with VEGF inhibition. For instance, **Jia *et al.*** [22] found similar reductions in retinal capillary density in patients with nAMD following anti-VEGF therapy, linking these changes to decreased oxygenation and subsequent atrophy of retinal cells. These structures may explain the gradual decline in visual function observed in long-term studies of anti-VEGF-treated patients. Such findings are crucial for understanding the potential trade-offs of prolonged therapy, as retinal atrophy may counteract the initial visual gains achieved by controlling neovascularization [22].

Despite regular anti-VEGF therapy, some patients continue to exhibit macular neovascularization [15]. This suggests that the treatment, although effective in reducing neovascular activity, may not completely prevent MNV proliferation in all patients. The persistence of hyperpermeability and fluid exudation highlights a potential limitation of anti-VEGF treatment in fully controlling disease progression in certain cases [16]. These findings support the hypothesis that MNV might represent a physiological repair mechanism to maintain retinal pigment epithelium and photoreceptor function.

This finding aligns with other studies in the field, which have noted that a subset of patients experiences continued or recurrent MNV despite consistent therapy. For instance, researchers such as **Freund *et al.*** [23] observed that while most patients show an initial reduction in neovascular activity, some exhibit persistent or recurrent fluid leakage, necessitating continuous monitoring and adjustments in treatment frequency. This variability in response has been attributed to several factors, including differences in VEGF isoforms, the presence of other growth factors, or the development of resistance to therapy over time.

In contrast, some studies have reported more complete suppression of neovascularization with less frequent recurrence in certain patient cohorts. For example, the HARBOR trial found that higher dosing regimens of anti-VEGF agents were associated with more durable responses, reducing the likelihood of persistent fluid or leakage. This comparison underscores the importance of tailoring treatment regimens to individual patient responses and suggests that more aggressive or combination approaches may be needed for those with persistent MNV despite standard therapy [24].

Visual acuity outcomes in patients receiving long-term anti-VEGF therapy generally show a modest decline over time. While most patients experience stabilized or improved vision in the initial years of treatment, a gradual deterioration in visual function often occurs after extended therapy, particularly beyond five years. This decline is largely attributed to the development of retinal atrophy or other structural changes in the retina, rather than the treatment's failure to control neovascularization [17,19]. This is consistent with findings from other studies, such as those reported by **Rofagha *et al.*** [25] in the SEVEN-UP study, where patients showed initial stabilization of vision but developed retinal atrophy, leading to visual decline over an extended follow-up period.

The findings on long-term anti-VEGF therapy in nAMD suggest important clinical implications for both patient management and therapeutic strategies. While anti-VEGF therapy is effective in stabilizing or improving visual acuity in the short term, the gradual visual decline over extended treatment periods underscores the need for careful long-term monitoring of patients. Clinicians should be aware that retinal atrophy and other structural changes may develop even with continued treatment, necessitating adjustments in therapy or exploring combination treatments to address these complications. Furthermore, identifying patients at risk for persistent macular neovascularization or atrophic changes may help in customizing treatment regimens, potentially improving visual outcomes.

STRENGTHS AND LIMITATIONS

One of the key strengths of this review is its comprehensive examination of long-term outcomes

associated with anti-VEGF therapy in nAMD. By consolidating findings from multiple long-term studies, the review provides a broad overview of how anti-VEGF therapy impacts both visual function and retinal structure over time. This holistic approach allows for a clearer understanding of the therapy's benefits and its limitations, offering valuable insights that can inform clinical decision-making and future research. Another strength is the emphasis on structural changes, such as retinal atrophy and vascular density alterations, which are often overlooked in discussions focusing solely on visual acuity outcomes. By highlighting these factors, the review provides a more nuanced perspective on the long-term effects of anti-VEGF treatment. Furthermore, the review incorporates findings from real-world studies in addition to clinical trials, giving a more practical understanding of how treatment outcomes manifest outside the controlled settings of clinical research.

Despite its comprehensive nature, the review does have limitations. One major limitation is the variability in the methodologies and follow-up periods of the studies analyzed. Long-term studies of anti-VEGF therapy often differ in terms of dosing schedules, patient demographics, and treatment regimens, which makes it difficult to draw definitive conclusions about long-term efficacy and safety. This heterogeneity limits the ability to generalize findings across all nAMD patient populations.

Another limitation is the reliance on studies that primarily focus on visual acuity and retinal structural outcomes, with limited attention to other important aspects such as patient quality of life, functional vision, and long-term systemic safety. Moreover, while the review highlights the emergence of retinal atrophy, it does not delve deeply into potential mechanisms behind this complication, leaving some gaps in understanding the underlying causes of long-term visual decline.

Finally, the review does not address the rapidly evolving landscape of nAMD treatments, including newer anti-VEGF agents, combination therapies, and extended-release formulations. As a result, some of the findings may already be partially outdated, especially given the introduction of more recent therapeutic options aimed at reducing treatment burden and potentially mitigating long-term complications.

CONCLUSION

Anti-VEGF therapy has significantly improved the prognosis for patients with nAMD, offering stabilization or improvement in vision and reducing the risk of severe visual loss. However, long-term outcomes highlight important challenges, such as the gradual development of retinal atrophy and the persistence of MNV in some patients. These findings suggest that while anti-VEGF therapy remains a cornerstone of nAMD management, future treatment strategies must address its limitations. Research into combination therapies, extended-release formulations, and novel agents that protect retinal structure will be critical to optimizing long-term outcomes and preserving vision for patients with nAMD.

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