International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 04 Issue 01 January 2024

Page No: 137-145

DOI: https://doi.org/10.47191/ijmscrs/v4-i01-31, Impact Factor: 6.597

Advances in the Treatment of Diabetic Retinopathy with Anti-VEGF Therapy

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ABSTRACT

Objective: This narrative review seeks to compare the advances and efficacy of various anti-VEGF therapies in the treatment of diabetic retinopathy, using the PICO format.

Methods: A comprehensive search of medical and scientific literature was conducted to identify studies investigating the efficacy of anti-VEGF therapies in the treatment of diabetic retinopathy. The PICO format guided the research question and review process. Accurate diagnosis, side effects, quality of life, and patient satisfaction were analyzed and compared for each treatment option.

Results: Anti-VEGF therapies were shown to be effective in reducing the progression of diabetic retinopathy, improving visual acuity and decreasing macular edema. Although generally safe, differences in side effect profiles were observed between the different anti-VEGF agents.

Conclusion: The selection of an appropriate Anti-VEGF therapy for diabetic retinopathy should consider accurate diagnosis, side effects, quality of life, and patient satisfaction. Although anti-VEGF therapies are promising, more research is needed to optimize their use and fully understand their benefits and limitations.

KEYWORDS: Diabetic Retinopathy, Vascular Endothelial Growth Factor A, Antibodies, Monoclonal, Humanized, Bevacizumab, Ranibizumab

ARTICLE DETAILS

Published On:
27 January 2024

Available on:
https://ijmscr.org/

INTRODUCTION

Diabetic retinopathy is a diabetes-related complication that affects the eyes. It is caused by damage to the blood vessels of light-sensitive tissue in the retina. As one of the leading causes of visual impairment and blindness, it has important public health implications, especially in regions with a high prevalence of diabetes [1] The main symptoms may include dark spots or threads floating in the vision (floaters), blurred or fluctuating vision, dark or empty areas in the vision, and vision loss. [1]

However, it is important to note that diabetic retinopathy often begins without any noticeable change in vision. Patients may not experience symptoms until the condition progresses.[1] Therefore, regular screening for diabetic retinopathy is recommended, especially since early detection and treatment can significantly reduce the risk of blindness. [2] It is diagnosed through different techniques such as ophthalmoscopy and fundus photography. A study that examined 795 eyes from a cohort of Oklahoma Indians with non-insulin-dependent diabetes mellitus found that there was an 86.3% concordance rate between ophthalmoscopy and non-mydriatic fundus photography performed through dilated pupils. The study indicated that fundus photography could be a comparable and cost-effective method for routine screening, provided there is an appropriate referral for people diagnosed with retinopathy.[3] Optical coherence tomography angiography (OCTA) is a noninvasive imaging modality that has demonstrated acceptable sensitivity and specificity for the diagnosis and classification of diabetic retinopathy. It can detect retinopathy at different stages and can even identify abnormalities before clinical changes in the fundus become apparent. [4]

Studies have demonstrated the involvement of VEGF in the pathogenesis of diabetic retinopathy by showing higher concentrations of VEGF in the ocular fluids of patients with proliferative diabetic retinopathy compared to those with

nonproliferative diabetic retinopathy and individuals without diabetic retinopathy. [5]

METHODOLOGY

A narrative review was conducted to explore advances in Anti-VEGF therapy for the treatment of diabetic retinopathy, focusing on accurate diagnosis, side effects, quality of life, and patient satisfaction, using the PICO format as a guide for the research question.

P: Patients with diabetic retinopathy; I: Anti-VEGF therapy; C: Comparison with other standard therapies/treatments; O: Accurate diagnosis, side effects, quality of life, patient satisfaction

An extensive search of scientific literature was carried out from 1 January 2010 to 30 April 2023, in recognised medical and scientific databases such as PubMed, EMBASE, Cochrane Library, CINAHL and Web of Science. We used the following search: (Anti-VEGF therapy, diabetic retinopathy diagnosis), OR (anti-VEGF therapy, diabetic retinopathy, side effects), OR (anti-VEGF therapy, diabetic retinopathy, quality of life), OR (anti-VEGF therapy, diabetic retinopathy, patient satisfaction), OR (anti-VEGF therapy, diabetic retinopathy efficacy). In addition, an extended literature search was conducted using the Research Rabbit search engine, and reference lists of included articles and relevant reviews were manually reviewed for further studies.

Studies were selected based on their relevance to the research question and their contribution to understanding the topic. The selection process will be described, including any general criteria used to determine the inclusion of studies. An overall assessment of the quality of the included studies will be provided, along with a discussion of any limitations that may affect the interpretation of the results.

We will use predefined questions and associated keywords guided by the PICO elements to ensure a more specific and targeted approach to the research question. These questions and keywords will be listed in a table and the corresponding subheading in the results section, where each question will be addressed. The presentation of results will be organized according to the predefined questions and the associated subheadings. Charts and graphs may be used to present the information in a clear and concise manner.

Information from the selected studies will be narratively synthesized, highlighting trends, similarities, and differences observed in the studies and discussing their relationship to the research question. The discussion in the narrative review will be broader and more flexible than in a systematic review, allowing for further interpretation and consideration of the practical and theoretical implications of the findings. An overall conclusion will be provided, summarizing the results and their implications for clinical practice, future research, and policy.

THEORETICAL FRAMEWORK

Based on a systematic review and meta-analysis that included 59 population-based studies, the global prevalence of diabetic retinopathy (DR) among people with diabetes was estimated to be 22.27% (95% confidence interval (CI), 19.73%-25.03%) as of March 2020. [6] Another analysis involving 35 studies involving 22,896 individuals with diabetes reported an overall prevalence of 34.6% for any DR, although different methodologies and population characteristics must be considered in the studies. [7] A study conducted in a hospital in northwestern Ethiopia found a DR prevalence of 34.1% among 331 diabetic patients. [8] Another cross-sectional study reported a prevalence of 36.3% among type 2 diabetic patients at the Northwest Amhara Comprehensive Specialized Hospitals in Ethiopia. [9] These various studies suggest that the overall prevalence of DR is significant, affecting a considerable proportion of people with diabetes worldwide.

Anti-VEGF Therapy

Vascular endothelial growth factors (VEGF) are a group of signaling proteins that are considered critical mediators of angiogenesis, which is the formation of new blood vessels and the increase in vascular permeability, hinting at the vital role in normal and pathological processes.

In diabetic retinopathy, VEGF plays a critical role in disease progression. [10] Diabetic retinopathy, a complication of diabetes, is characterized by damage to the blood vessels in the retina, leading to ischemia and subsequently the formation of new, fragile blood vessels in an attempt to restore blood supply to the retina. Studies have demonstrated the involvement of VEGF in the pathogenesis of diabetic retinopathy by showing higher concentrations of VEGF in the ocular fluids of patients with proliferative diabetic retinopathy compared to those with nonproliferative diabetic retinopathy and individuals without diabetic retinopathy. [11]

In addition, genetic polymorphisms in the VEGF gene have been associated with the risk of developing DR. Polymorphisms such as rs2146323, [12] C(-634)G, [13] and +405 G/C [14] They have been studied extensively in several populations, indicating that certain genotypic variants may increase susceptibility to diabetic retinopathy. For example, studies have shown a significant association between the C allele of the C(-634)G polymorphism in the VEGF gene and an increased risk of diabetic retinopathy. [15] Similarly, the VEGF +405 GG genotype was found to be an independent predictor of the risk of proliferative diabetic retinopathy in an Iranian population. [16]

In summary, VEGF is intimately linked to the development and progression of diabetic retinopathy, where its increased expression due to hypoxia-induced retinal ischemia can lead to the pathological neovascularization and leakage characteristic of this complication of diabetes. Genetic variations in the VEGF gene may affect individual

susceptibility to DR and may serve as potential markers of disease risk. [17] [18]

Anti-VEGF treatments work by targeting pathogenic vascular endothelial growth factor (VEGF), which is upregulated in this condition. VEGF plays a crucial role in promoting neovascularization and increasing vascular permeability, leading to aspects of diabetic retinopathy such as diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).

With these data we can present specific insights from studies on the role and efficacy of anti-VEGF treatments in diabetic retinopathy.

Anti-VEGF intravitreal therapy is beneficial for central DME in patients with type 1 diabetes, as it leads to a significant increase in visual acuity. Both baseline and long-term visual improvements were observed in patients treated with anti-VEGF alone or in combination with macular laser compared to the observation or macular laser groups. These results were observed over a 15-year period, indicating the effectiveness of anti-VEGF in stabilizing and improving vision in patients with central DME. [19]

Serum VEGF concentrations in patients decrease after intravitreal injections of Avastin (bevacizumab), indicating a systemic effect of anti-VEGF treatments. These changes in VEGF levels align with the serum and vitreous pharmacokinetics of bevacizumab, which may provide insight into its mechanism and timing of action after administration of diabetic retinopathy. [20]

In addition, a new specific antibody, faricimab, which targets both angiopoietin-2 and VEGF-A, has been shown to have double efficacy. The phase 2 BOULEVARD trial indicates that faricimab may lead to statistically superior visual acuity gains compared to ranibizumab in treatment-naïve patients. Faricimab also demonstrated reductions in central subfield thickness and improvements in diabetic retinopathy severity scale score, suggesting the therapeutic benefit of simultaneously inhibiting angiopoietin-2 and VEGF-A in the treatment of DME. [21] In summary, anti-VEGF treatments work effectively for diabetic retinopathy by targeting VEGF-driven pathological processes, leading to improvements in visual acuity, reduction of macular edema, and decreased need for surgical interventions with positive perioperative outcomes.

Types of Anti-VEGF Agents

Several anti-vascular endothelial growth factor (anti-VEGF) agents are now available for the treatment of DR, one example being aflibercept, of which a study comparing changes in DR severity during treatment with aflibercept, bevacizumab, or ranibizumab for diabetic macular edema (DME) showed that aflibercept was associated with greater improvement at 1 and 2 years in participants with RDP at baseline; [22] bevacizumab: While less improvement in DR was seen with bevacizumab at 1 year compared with aflibercept or ranibizumab, bevacizumab remains a common medication used to treat DR, despite not being approved by the U.S. Food and Drug Administration. [23], [24]

for ophthalmic conditions finally, ranibizumab showed improvement in DR and was associated with low rates of DR worsening. This drug was also compared in a pre-planned secondary analysis of a randomized trial for the treatment of DME [25]

It should be noted that the choice of anti-VEGF treatment may be influenced by the specific stage of DR, as different agents have shown varying degrees of efficacy in improving proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR) [26] [27]

Evolution of Anti-VEGF Therapy in Diabetic Retinopathy

With the development of this topic, the historical evolution of anti-VEGF treatments for diabetic retinopathy has been found. a study conducted in the North Ostrobothnia Hospital District evaluated the real-world visual outcomes of diabetic macular edema (DME) treatment in patients with type 1 diabetes (T1D) from 2006 to 2020, [28] The study found that treatment for DME has revolutionized over the past 15 years with the introduction of intravitreal anti-VEGF agents resulting in patients with type 1 diabetes and central DME who received anti-VEGF alone or in combination with macular laser showed significant visual improvements, however, another study looked at the systemic safety of intravitreal anti-VEGF agents in patients with diabetes, [29] The study found that the 5-year cumulative incidence of any systemic adverse event was higher in patients who received anti-VEGF injections compared to those who did not. [[30]However, it's important to note that the study didn't focus specifically on diabetic retinopathy, but on diabetes patients in general. [31]

A retrospective cohort study using administrative medical claims data from a U.S. national insurer looked at trends in EMD care, [32] The study found that the use of anti-VEGF treatments, along with focal laser therapy, increased over time. [33] However, the use of anti-VEGF agents was even less frequent than focal laser therapy, despite the proven superior visual results of anti-VEGF agents[33]

The historical evolution of anti-VEGF treatments for diabetic retinopathy has shown significant advances in terms of visual outcomes and treatment stability, the use of anti-VEGF agents may be associated with an increased likelihood of systemic adverse events in patients with diabetes. We can conclude that use of anti-VEGF treatments has increased over time, but focal laser therapy is still more prevalent

Diabetic Retinopathy Treatment Success Rates

Advances in anti-VEGF therapy have had a positive impact on the treatment of diabetic retinopathy. A Retrospective Multicenter Case Series[34] showed that patients with diabetic retinopathy who underwent exclusive anti-VEGF therapy and experienced treatment discontinuation had marked disease progression and potentially devastating visual consequences.

This highlights the importance of consistent and uninterrupted treatment.

The system examined the impact of an interactive continuing education (QE) initiative [35] in the management of retinal disease, including diabetic retinopathy. The study found that participants who participated in the CD initiative demonstrated significant improvements in knowledge and competence related to the early identification, treatment, and importance of anti-VEGF therapy. The same study it also analyzed medical claims data and found that the use of anti-VEGF agents for retinal conditions increased significantly among ophthalmologists and retinal specialists who participated in the CE initiative, compared to a control group of non-students. This suggests that better knowledge and education about anti-VEGF therapy may lead to changes in practice. [36]

Overall, advances in anti-VEGF therapy, along with improved education and knowledge, have led to better outcomes and increased use of these therapies in the treatment of diabetic retinopathy

Clinical Studies and Scientific Evidence

The Diabetic Retinopathy Clinical Research Network conducted a randomized clinical trial (RCT) of comparative effectiveness. [37] The study evaluated three anti-VEGF agents: aflibercept, bevacizumab, and ranibizumab for the treatment of diabetic macular edema (DME) that affects the center of the retina and is associated with loss of visual acuity. The results showed that all three agents led to an improvement in visual acuity in eyes with DME, with aflibercept showing the greatest benefit in patients with worse visual acuity at the start of treatment. - A secondary analysis of a randomized clinical trial compared changes in the severity of diabetic retinopathy (DR) during treatment with aflibercept, bevacizumab, or ranibizumab for DME. [38]

The study found that all three anti-VEGF agents led to improvements in DR severity in participants with non-proliferative DR (NPDR) and proliferative DR (PDR) at 1 and 2 years. Aflibercept showed greater improvement in DR severity compared to bevacizumab at 1 year in the eyes of NPDR, and in the smaller subgroup of participants with RDT at baseline.

Both studies concluded that all three anti-VEGF treatments were associated with low rates of DR worsening and can be considered effective in the treatment of diabetic retinopathy. However, it is important to note that there are differences in the results of visual acuity and improvement in DR severity between the three agents. More research is needed to assess the effectiveness of different treatment regimens and the use of repackaged bevacizumab.

It has been proven that anti-VEGF pharmacotherapy, administered by intravitreal injection, is a safe and effective treatment for diabetic macular oedema (DME) for 2 years. [39]

Several studies provide Tier I evidence for the use of intravitreal ranibizumab, alone or in combination with other treatments, for DME. [40]

Similarly, we provide Level I evidence for the use of intravitreal pegaptanib sodium for DME. [41]Most of the studies reviewed do not provide information on long-term outcomes (i.e. beyond 2 years) or comparative efficacy of anti-VEGF pharmacotherapies for DME. More evidence is needed to support the long-term safety and comparative efficacy of anti-VEGF therapies for diabetic retinopathy.

It is also worth noting that the long-term safety and comparative efficacy of anti-VEGF therapies for diabetic retinopathy remain areas that require further investigation. These findings suggest that anti-VEGF therapy shows promise as a safe and effective treatment for diabetic retinopathy, but more research is needed to fully understand its long-term safety and efficacy.

Comparison with Other Treatment Modalities

Anti-VEGF therapy has been shown to be effective for the treatment of diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD).[42] A brief summary has been prepared that anti-VEGF therapy with other treatment options for diabetic retinopathy begins with a A study in which aflibercept, bevacizumab, and ranibizumab were taken for the treatment of DME. On average, all three anti-VEGF agents led to improved visual acuity in eyes with DME affecting the center of the retina and impaired visual acuity. Aflibercept was found to have a greater visual acuity benefit compared to bevacizumab and ranibizumab, especially in eyes with poorer visual acuity at the start of therapy. The study concluded that care should be taken when extrapolating the results of this study to different treatment regimens.

Another study evaluated the management patterns and outcomes of anti-VEGF therapy for nAMD. It found that patients who received anti-VEGF treatment made an average of 6.0 injections during the first 12 months. [43]

Visual acuity and anatomical results varied depending on the anti-VEGF agent used, with approximately 15-19% of eyes showing a gain of more than 10 letters and 13-15% showing a loss of more than 10 letters. The number of anti-VEGF injections was associated with improvements in visual acuity and reduction in central retinal thickness.

With regard to laser photocoagulation or vitrectomy as treatment options for diabetic retinopathy, the first search results provided do not directly compare these options to anti-VEGF therapy. However, it is important to note that anti-VEGF therapy has become the standard of care for the treatment of DME and has demonstrated significant benefits in improving visual acuity and reducing macular edema.

In summary, based on the available evidence, anti-VEGF therapy appears to be an effective treatment option for diabetic retinopathy, specifically for DME. More research is needed to directly compare anti-VEGF therapy with laser

photocoagulation or vitrectomy to determine the optimal treatment approach for diabetic retinopathy.

We can compare anti-VEGF therapy with other treatment options for diabetic retinopathy, such as laser photocoagulation or vitrectomy.

Anti-VEGF therapy combined with panretinal photocoagulation (PRP) was found to significantly improve visual acuity, reduce central foveal thickness, and decrease microaneurysms in patients with high-risk proliferative diabetic retinopathy (PDR)[44]

Another study claims that anti-VEGF therapy is superior to laser photocoagulation for treating moderate to severe visual impairment caused by diabetic macular edema (DME) [45] It is important to note that the use of anti-VEGF therapy can lead to a higher rate of recurrence and requires vigilant and prolonged follow-up. [46]

Laser photocoagulation has been the standard treatment for DME for nearly three decades [47] showed no significant improvements in visual acuity, central foveal thickness, or microaneurysms in patients with high-risk PDR. [48] Although laser photocoagulation is effective, anti-VEGF therapy has shown superior results in terms of visual improvement and safety.[49]

Anti-VEGF treatment, specifically aflibercept, combined with panretinal photocoagulation, has shown significant improvements in visual acuity, central foveal thickness, and microaneurysms in high-risk PDR patients. - Anti-VEGF therapy is considered superior to laser photocoagulation for the treatment of moderate to severe visual impairment caused by DME. - Laser photocoagulation has been the standard treatment for DME, but anti-VEGF therapy has been shown to provide better outcomes. - More research is needed to evaluate the efficacy of vitrectomy as a treatment

Challenges and Limitations of Anti-VEGF Therapy

The main current challenges and limitations in the use of anti-VEGF therapy for diabetic retinopathy include limited anatomical and visual acuity improvements: A retrospective observational cohort study found that anti-VEGF therapy showed moderate and limited anatomical improvements in visual acuity in patients with neovascular age-related macular degeneration (AMD). The study reported that mean central retinal thickness decreased by -48 μm, and mean visual acuity increased by only +0.6 letters after 12 months of treatment. Another study showed variable responses to anti-VEGF therapy between different drugs. After 12 months of treatment, [50] Some eyes experienced a gain of more than 10 letters in visual acuity, while others showed a loss of more than 10 letters. The proportion of eyes that showed significant improvement varied with different anti-VEGF agents. As a result, the number of anti-VEGF injections received by patients had an impact on treatment outcomes. One study showed that eyes that received 7 or more injections had a greater increase in visual acuity compared to those that received fewer injections. Similarly, the reduction in central retinal thickness tended to be greater with increasing the number of injections.

Concerns have been raised regarding the potential renal effects of intravitreal anti-VEGF therapy. [51] A retrospective cohort study found that some patients with diabetic macular edema experienced worsening glomerular filtration rate (eGFR) and microalbuminuria (MicA) after anti-VEGF therapy. However, the study did not find a significant relationship between the number of injections or the type of drug

Treatment interruptions leading to disease progression: Patients with diabetic retinopathy who are treated exclusively with anti-VEGF therapy and experience treatment interruptions may experience severe disease progression with potential visual consequences. [52]

Patients who temporarily missed follow-up experienced complications such as vitreous hemorrhage, neovascular glaucoma, and traction retinal detachment. These complications resulted in a significant loss of visual acuity in most eyes.

Future of Anti-VEGF Therapy in Diabetic Retinopathy

The following innovations could improve the management and outcomes of patients with diabetic retinopathy in anti-VEGF therapy: Micropulse subthreshold laser (MPSL) combined with anti-VEGF therapy has been shown to be as effective as anti-VEGF therapy alone in improving best-corrected visual acuity (BCVA) and central macular thickness in patients with diabetic macular edema (DME).

Combined MPSL and anti-VEGF therapy requires significantly fewer anti-VEGF injections compared to anti-VEGF therapy alone, which could improve the overall treatment of DME in terms of cost-effectiveness. [53]

An immersive, interactive medical education initiative has demonstrated significant advances in knowledge and competence among retinal disease care providers, including ophthalmologists and retinal specialists, resulting in changes in practice-related behaviors such as proper consideration and increased uptake of anti-VEGF therapies recommended by the guidelines. [54]

This educational initiative also resulted in increased use of anti-VEGF injections for retinal conditions among participating ophthalmologists and retinal specialists compared to non-students, indicating a positive impact on treatment behavior. [55]

It is crucial to avoid unintentional treatment interruptions in patients treated exclusively with anti-VEGF therapy for diabetic retinopathy, as these interruptions can lead to marked disease progression and potentially devastating visual consequences. Patients with treatment interruptions may experience complications such as vitreous hemorrhage, neovascular glaucoma, and traction retinal detachment, ultimately resulting in irreversible blindness. [56]

These innovations can contribute to improving the management and outcomes of patients with diabetic retinopathy undergoing anti-VEGF therapy by providing alternative treatment options, reducing the number of injections needed, improving healthcare providers' knowledge and competence in guideline-based management of retinal disease, and emphasizing the importance of consistent adherence to treatment to prevent the progression of disease and complications.

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