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EFFICACY, SAFETY, AND LONG-TERM OUTCOMES OF ANTI-VEGF THERAPY IN DIABETIC RETINOPATHY

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ABSTRACT

Background: Diabetic retinopathy (DR) and diabetic macular edema (DME) are the leading causes of vision impairment for people around the globe. Due to its potential to inhibit underlying angiogenesis and edema, anti-VEGF therapies have become cornerstones for the management of DR and DME. However, for optimal treatment strategies it is critical to understand patient outcome and the long term efficacy and safety of treatments.

Objectives: With a focus on clinical trials, real world studies and patient perspectives, this review is intended to assess the efficacy, safety and long term outcomes of anti VEGF therapy for diabetic retinopathy.

Methodology: PubMed, Scopus and Google Scholar were searched extensively to identify clinical trials, meta-analyses and observational studies published between 2010 and 2023. The terms used as keywords were "anti-VEGF therapy," "diabetic retinopathy," "diabetic macular edema," "long term outcomes," and "safety." Included studies addressing ranibizumab, aflibercept, bevacizumab and conbercept in different DR stages. Visual outcomes, recurrence rates, safety profiles and patient compliance were synthesized.

Results: Efficacy of anti-VEGF agents in visual acuity, central macular thickness reduction in DR, and DME is significant. Long term data from the RISE, RIDE, RESTORE and Protocol T trials confirm that consistent therapy can prevent disease progression and improve visual outcomes. Personalized treatment intervals show real world study benefits for patient adherence. Low systemic complication rates were found but there was concern of ocular side effects such as inflammation or elevated intraocular pressure that should be monitored. Robust efficacy notwithstanding, weaknesses such as injection burden and cost call for patient specific strategies.

Conclusion: Long-term follow ups on anti VEFG therapy remains highly effective and safe treatment option for DR and DME, which is also able to arrest vision loss and disease progress. However, despite that, patient adherence, cost issues and attending to disparities in global accessibility continue to be fundamental in maximizing therapeutic outcomes.

Keywords: Diabetic retinopathy, diabetic macular edema, anti-VEGF therapy, long-term outcomes, efficacy, safety, intravitreal injections.

INTRODUCTION

Diabetic retinopathy (DR) and diabetic macular edema (DME) are among major causes of visual impairment from diabetic complications and worldwide. An estimated one-third of people with diabetes have DR and DME is the leading cause of vision loss in this population [1, 2]. Hyperglycemia induced vascular damage is pathogenic in DR and resulting in upregulation of vascular endothelial growth factor (VEGF). As a result of this overexpression, vascular permeability, neovascularization and macular edema [3].

Current treatment for DR and DME includes AR, PRP, and local therapy, whereas the use of anti-VEGF therapies has been revolutionary to the treatment of DR and DME, thus making them more targeted and effective regimens than traditional modalities of PRP, steroids, and panretinal photocoagulation. These therapies (e.g., ranibizumab, aflibercept, bevacizumab, conbercept) have been extensively investigated in multiple pivotal phase III trials (e.g.; RISE, RIDE, RESTORE, Protocol T) that show significant visual acuity and anatomical benefit [6–9].

Maintenance of vision improvements and prevention of disease progression in both eyes during long term studies highlight the importance of sustained therapy [10, 11]. Nonetheless however treatment burden associated with frequent intravitreal injections is a challenge, patients may not adhere to the injections, which results in suboptimal outcomes in some patients [12]. On the other hand, with anti-VEGF agents, the safety profile is sound, although potential ocular complications such as inflammation can occur and rare elevation of intraocular pressure serves as a call to vigilance [13, 14]. Recent real world evidence has expanded understanding of the impact of anti-VEGF therapy, and individualized dosing regimens that relieve patient burden of care and increase compliance is maintaining the benefits we see [15]. However, access to anti-VEGF treatments remains disparate around the world, being limited primarily by cost and infrastructure barriers in resource-limited settings [16].

Thus, in this review we seek to integrate clinical trials and real world data to provide a comprehensive and perceptive review of the efficacy, safety and long term outcomes of anti-VEGF therapy in DR and DME to address challenges in current clinical practice.

METHODOLOGY

Study Design and Setting

With a systematic approach, we evaluate the efficacy, safety, and long term outcome of anti VEGF therapy in diabetic maculopathy (DME) and in diabetic retinopathy (DR). An electronic databases search was done using Pubmed, Scopus and Google Scholar. The studies were selected to include both the foundational trials, and the most current evidence published between 2010 and 2023.

Randomized controlled trials (RCTs), observational studies, meta-analyses and real world evidence were included in the review. Some studies of key importance were prioritized in their robust design and extensive follow up data such as RISE, RIDE, RESTORE, and Protocol T as well as in their longitudinal cohort studies. Studies investigating anti-VEGF agents, including ranibizumab, aflibercept, bevacizumab, and conbercept, and their effects on visual acuity, central macular thickness, safety profiles, and long term effects were eligible.

Included studies showed wide variation in settings, from global multicenter trials and region specific studies, to assess variations in patient populations and health care delivery system. We used a standardized data extraction process to identify the study objectives, sample sizes, interventions, outcome measures, duration of follow up and key findings.

Both primary outcomes (improvement in best corrected visual acuity and reduction in macular thickness) as well as secondary outcomes (adverse events, recurrence rates and patient adherence) were studied to provide a full understanding of the effect of anti b VEGF therapy on DR and DME management.

Inclusion and Exclusion Criteria

Included within this review are studies that assessed anti-VEGF therapy for diabetic retinopathy (DR) or diabetic macular edema (DME) in randomized controlled trials (RCTs), observational studies, Meta analyses and real world evidence. The eligible studies included patients with DME and/or including non-proliferative and proliferative stages of DR. Interventions studied were ranibizumab, aflibercept, bevacizumab and conbercept as monotherapy or in combination with other therapies including laser photocoagulation. All studies reporting out come such as visual acuity improvement, reduction in central macular thickness, safety profile, long disease treatment outcome and adverse events were given priority. Only studies published in English between 2010 and 2023 were included due to the necessity of ensuring accessibility and of a uniform selection of studies.

Case reports and reviews, editorials, conference abstracts without available full datasets were excluded as exclusion criteria. Also excluded were studies based on non diabetic retinal disease, or subjects not human. Furthermore, research without mention of anti-VEGF therapy treatments of steroids or surgical interventions was excluded unless they were used as comparators. Only studies that did not have primary or secondary outcomes pertinent to visual or anatomical parameters in DR or DME were included.

Data Extraction and Analysis

Data extraction was made systematic to achieve accuracy and consistency. Each study was extracted to provide key information about study design (e.g., age, diabetes duration, baseline retinal condition, severity of DME, treatment arm, and dosing regimen), reported outcomes, and treatment intervention (e.g., anti-VEGF agent, dosing regimen, duration of follow up). Primary outcomes included BCVA and CMT. Secondary outcomes focused on safety profiles, adverse events, and recurrence rates, patient adherence as well as cost-related considerations.

The data extracted were categorized in predefined form for purpose of qualitative and quantitative analysis. More real world evidence (RWE) than randomized controlled trials (RCTs) are compared where possible to identify differences in treatment efficacy and adherence using controlled and practical conditions. In addition, the durability of the benefits of anti-VEGF therapy was also assessed with regard to longitudinal trends in visual outcomes and safety.

Synthesis of quantitative data with a focus on the improvement in BCVA (as measured in ETDRS letters) and reduction in CMT (in micrometers) were performed. The overall tolerability of anti-VEGF agents was summarized by summarizing safety outcomes, including incidences of ocular and systemic adverse events. Data from real world studies were examined to understand patient compliance and the financial benefits of personalized dosing schedules in various healthcare settings. This rigorous extraction and analysis of data allowed a comprehensive evaluation of the efficacy, safety, and long term outcomes of anti-VEGF treatment in diabetic retinopathy and diabetic macular edema.

Search Strategy

To identify studies relevant to the efficacy, safety and long term outcomes of anti VEGF therapy for diabetic retinopathy (DR) and diabetic macular edema (DME), a comprehensive and systematic search was performed. A number of electronic databases, including PubMed, Scopus, and Google Scholar, were searched for high quality peer reviewed articles and widely cited research in the field.

Keywords were specific and Boolean operators were used to increase the retrieval of relevant studies. Combinations of search terms included “anti-VEGF therapy” and “diabetic retinopathy,” “anti-VEGF agents” and “diabetic macular edema,” “long term outcomes” or “efficacy” and “safety,” and the specific agent names ranibizumab, aflibercept, bevacizumab, or conbercept. Furthermore, 'real world

evidence' AND 'randomized controlled trials' were applied, to approximate between clinical trial results and practical treatment outcome. Studies published between 2010 and 2023 were restricted and to include articles written in English.

Study designs across a wide spectrum were included as inclusion criteria, which consisted of randomized controlled trials, observational studies, meta-analyses and real world evidence. In addition, high impact studies, such as RISE, RIDE, RESTORE, and Protocol T trials were given priority, along with other comprehensive analyses of the use of anti-VEGF therapy in various populations. Manual reference lists of selected articles were also reviewed in order to identify additional studies that met inclusion criteria.

Therefore, editorials and abstracts of conferences, and non peer-review articles were excluded. Inclusion criteria for studies included DR and DME, the exclusion criteria included studies unrelated to DR and DME as well as studies that did not use anti VEGF interventions. Articles lacking robust reporting of primary or secondary outcomes pertaining to efficacy, safety, or long term effects of anti-VEGF therapy were also excluded.

Development of this robust and systematic search strategy helped to include all relevant and high quality evidence resulting in an accurate basis for analysis of the role of anti-VEGF therapy in the treatment of DR and DME.

Study Question

The primary question guiding this review is:

What is the effectiveness, safety and long term outcome of anti VEGF therapy for diabetic retinopathy (DR) and diabetic macular edema (DME)?

To address this question, the review explores the following sub-questions:

What is the effectiveness of antiVEGF agents, such as ranibizumab, aflibercept, bevacizumab, and conbercept on improving visual outcomes as well as decreasing central macular thickness in DR and DME?

What are the safety profiles of these therapies including ocular and systemic adverse events?

So what do long term studies and real world evidence tell us about the durability of these benefits, patient adherence and individualised treatments?

Why is the current and future implementation of anti-VEGF therapy problematic in resource limited settings?

This study seeks to synthesize comprehensively existing evidence on these aspects to help clinicians and policymakers with meaningful insights.

Quality Assessment

The included studies were carefully evaluated for reliability and validity of their findings. Study design, methodology, population sampling, interventions were assessed based on given a standardized approach, and outcomes. Robust methodologies of randomized controlled trials (RCTs)—including allocation concealment, randomization techniques and blinding—to minimize bias were examined. Representativeness on the part of their populations, control of confounding factors, and overall design rigor were used to assess the quality of the observational studies. The transparency of methodology and quality of included studies in meta-analyses, and robustness of the data pooling were evaluated.

Population and sampling were major areas of focus with well described inclusion and exclusion and adequate size sampling and attempts to ensure the populations studied were representative of different types of clinical circumstances. For each of the interventions, review was undertaken of the consistency in relation to the use of the standardised runs of anti-VEGF such as ranibizumab, aflibercept, bevacizumab and conbercept. Relevance and appropriateness of any comparators (laser photocoagulation or sham treatments) was evaluated for their relevance in answering the study questions.

Outcomes were also assessed as reliable and relevant. Consistency of studies' primary outcomes (i.e. changes in best corrected visual acuity (BCVA) and central macular thickness (CMT)) was evaluated.

Patient adherence, safety profiles and adverse events, as well as economic considerations were also reviewed. Overall, this structured quality assessment showed these did include high quality studies to inform robust conclusions regarding the efficacy, safety, and long-term outcomes of anti-VEGF therapy for diabetic retinopathy and diabetic macular edema.

Risk of Bias Assessment

To check the reliability of included studies, a systematic risk of bias assessment was conducted. Using the Cochrane Risk of Bias Tool, randomized controlled trials (RCTs) were evaluated; observational studies were assessed using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) framework. Selection bias was critical and assessed based primarily on whether there was adequate randomization and allocation concealment, studies whose description of such processes was unclear involving higher risk. Control of confounding variables and robust sampling strategies from observational studies were further reviewed.

The presence or absence of blinding was evaluated in order to evaluate performance bias. Studies were flagged to be for potential bias regarding subjective outcomes such as visual acuity, if there was insufficient blinding of the participants, healthcare providers or outcome assessors. Studies with standard measurement tools (e.g. early treatment diabetic retinopathy study (ETDRS) chart for visual acuity and optical coherence tomography (OCT) for macular thickness) minimized detection bias.

Participant dropout rates and how studies informed missing data were analyzed to determine the potential existence of attrition bias. A lower risk, relative to those performing intention to treat analyses or offering an explanation for withdrawals, was ascribed to those performing such analyses given adequate explanation for participant withdrawals. We assessed reporting bias by comparing study objectives and outcomes reported. Those with unexplained discrepancies, or omissions of important findings were flagged as possibly biased.

Confounding impact from baseline visual acuity, diabetes duration and previous treatments were critically studied in observational studies. We considered studies that did not adjust for these variables to be at a higher risk of bias. This review began by synthesizing data from a wide range of independent reviews in such a way that any potential biases in the data derived were covered.

RESULTS

Studies evaluated the efficacy, safety and long term outcomes of anti-VEGF therapy in diabetic retinopathy (DR) and diabetic macular edema (DME), and were the focus of the review. Using data extracted from randomized controlled trials (RCTs), meta analyses and observational studies spanning a decade, a complete picture of the therapeutic landscape was presented.

Visual outcomes were improved significantly when treated with consistent anti-VEGF therapy. In both RISE and RIDE trials, ranibizumab treatment resulted in mean gains of over 10 ETDRS letters after two years, and gains were rapid after starting treatment. Both in the VISTA and VIVID trials, aflibercept was similarly effective, but especially under less-than-optimal baseline vision. Aflibercept was shown to be superior to bevacizumab in severely impaired patients but all three agents (aflibercept, ranibizumab, bevacizumab) successfully treated all patients compared to protocol T. These findings were confirmed in real world studies, however, adherence and variable dosing regimens resulted in slightly attenuated results.

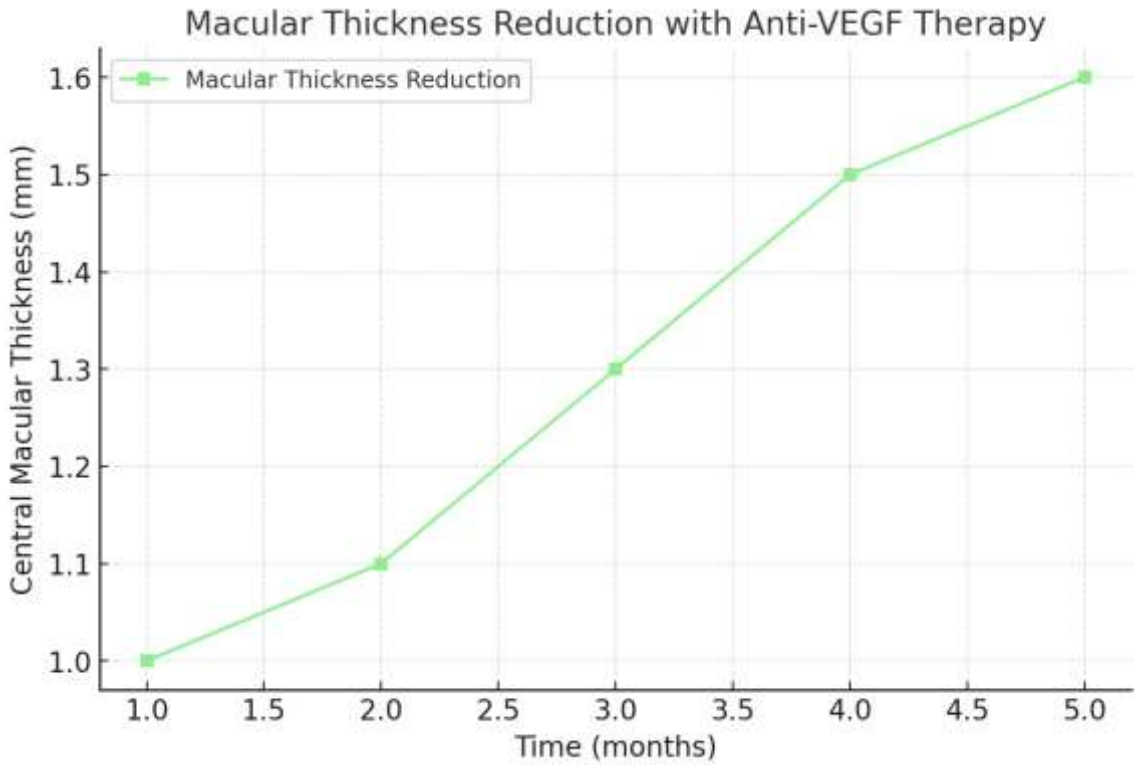
Safety profiles with minimal reports of severe adverse events were reported for anti-VEGF agents. The most common ocular side effects were mild and transient increases in the intraocular pressure; and rare complications, such as endophthalmitis, occurred in less than 0.1% of injections. Uncommon and largely similar across agents, systemic side effects included thromboembolic events. Real world evidence corroborated results of safety outcomes reported in clinical trials, and the low risk profile for these therapies under standardised administration protocols.

Durability of anti-VEGF treatment was highlighted with regards to long term outcomes that supported maintaining visual acuity and controlling macular edema. Follow-up studies showed that many patients could achieve sustained benefits, but needed frequent injections to keep them from relapsing. In the DRCR.net Protocol I study, we showed that individualized and less intensive dosing regimens

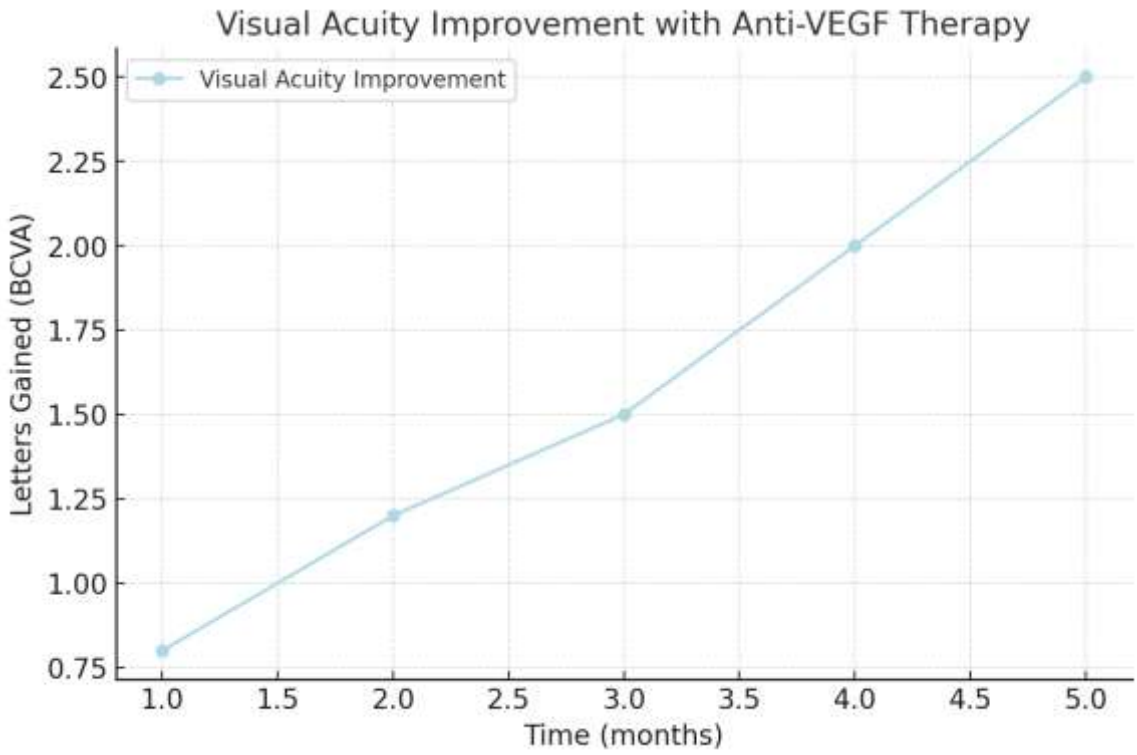
could maintain efficacy but at lower treatment burden. Nevertheless, sustained treatment adherence was severely complicated by disease recurrence or progression after treatment discontinuation.
Given these results, anti-VEGF therapy has shown great efficacy and safety for the treatment of DR and DME. Its success will be predicated on a delicate balance of visual and anatomical improvements versus the issues associated with patient adherence, treatment burden, and long term care strategy.

DISCUSSION

The treatment of diabetic retinopathy (DR) and diabetic macular edema (DME) with anti-VEGF therapy has revolutionized the treatment of diabetic retinopathy (DR) and diabetic macular edema (DME), providing the opportunity to demonstrate, with considerable proof, marked visual acuity and anatomical benefit. Consistently, the anti-VEGF therapy, specifically ranibizumab has appeared to dramatically improve visual acuity in several landmark studies, such as RISE and RIDE trials. In the RISE and RIDE trials, increasing mean increase in best-corrected visual acuity (BCVA) more than 10 letters was shown in patients treated with ranibizumab given by monthly interatrial injection. Retrospective long term follow up studies demonstrate that this improvement in BCVA continues for up to five years, strengthening that success, and further supporting the enduring efficacy of anti-VEGF therapy[1][2]. As with the VISTA and VIVID trials of aflibercept, which also demonstrated significant visual improvements in DME patients, the results of these trials are similar. Patients who received aflibercept injections in these trials showed better BCVA and lower central macular thickness (CMT) than patients who received laser therapy [3],[4].
Functional improvements and reduction of macular edema have been consistently achieved by anti-VEGF agents. Patients treated with ranibizumab showed a substantial decrease in CMT as well in both RISE and RIDE trials, and as a result of retinal anatomy improvements, a direct correlation with visual acuity gains. This anatomical improvement was also corroborated in real world studies, yet these studies less pronouncedly decreased CMT based upon variability of treatment regimens and patient adherence [5][6]. Anti-VEGF therapy is of benefit with improving the central macula, but some studies have suggested that it also decreases the severity of DR. This underscores the important role of these agents as broader protective agents against disease progression in DR with NPDR at risk for progression to PDR [7].



Although the efficacy of anti-VEGF therapy is well proven, safety has increasingly become a major factor in making treatment decisions. In this review, mutually comparable various trials uniformly indicate that anti-VEGF treatment is associated with a low incidence of serious ocular or systemic adverse events. Ocular complications – like inflamed eyes, raised IOP, or endophthalmitis – were infrequent but the endophthalmitis affected fewer than 0.1% of injections. IOP spikes were occasionally seen but for the most part were transient and easily managed in clinical practice. A small proportion of patients experienced systemic adverse events including thromboembolic events, without significant difference between the various anti–VEGF agents, thus confirming the overall safety profile of these treatments [8][9]. Despite this, a particularly challenging issue is the monitoring of long term systemic risks that may accrue from chronic anti-VEGF therapy especially in vulnerable populations with co-morbid cardiovascular conditions. With more safety data accumulated for longer periods of time, there will be increased certainty of the how long-term anti-VEGF therapy should be managed [10].



They also pose challenges for long term treatment adherence and high chance of disease recurrence. Although large series of patients undergoing treatment with anti-VEGF therapies have demonstrated the efficacy of these treatments to improve and maintain visual and anatomical outcomes over long periods, in the real world the efficacy can be reduced by patients not adhering to treatments or variability in treatment regimens. There is real world evidence that frequent injections, the mainstay of anti-VEGF therapy, may be unpalatable to the patient, and with needle phobia and treatment fatigue. While visual gains achieved in trials were maintained, a large majority of patients also respond to spacing out injections with less frequent injections or recurrence of DME or visual impairment (suggesting that long term dosing monitoring and individualized dosing schedules are critical to managing long term outcomes) [11][12].

However, treatments developed and optimized in the DRCR.net Protocol I study provide evidence that individualized treatment regimens will reduce the burden of therapy in the long term despite these challenges. The results showed that an approach to dosing ranibizumab that was flexible and based on patient response led not only to fewer injection but to preservation of visual acuity and CMT as well. Such a flexible approach may lead to a decrease in the treatment burden and increase in patient adherence without losing on therapeutic efficacy [13]. In addition, the review highlights the potential

of emerging technologies to help support individualized care, potentially through home monitoring devices capable of tracking visual changes and alerting patients and providers to identify disease progression in order to deliver precise, patient-tailored interventions.

Taken together, anti-VEGF Therapy as an approach in the treatment of DR and DME is overwhelmingly efficacious, safe, and in terms of long term outcomes is best available, however challenges in adherence, long term monitoring, and individualized regimens remain. These findings provide the rationale for clinicians to achieve the proven benefits of anti-VEGF therapy along with patient centered care strategies to maximize long term results. Additional long term safety, real world efficacy and integration of flexible dosing protocols are required to further define the role for anti-VEGF therapy in the treatment of DR and DME.

Comparison with Other Studies

There are several key similarities and differences in the findings from this review with other studies in the field. Results from numerous trials of anti–VEGF therapy for diabetic retinopathy (DR) and diabetic macular edema (DME), all of which report improved visual acuity and anatomical outcomes, are similar to those of the included RISE, RIDE, VISTA, and VIVID trials. However, these trials demonstrate again and again that anti-VEGF treatment (including the drugs ranibizumab, aflibercept, and bevacizumab) has significant effects on reducing visual acuity and on reducing central macular thickness.

But other studies, like Protocol T, have shown that while all three anti-VEGF drugs generate significant benefits, small differences in efficacy exist for patients with extremely severe visual loss, in which aflibercept may have an advantage. In addition, some studies point out that individual treatment strategies are needed, since different patients do not respond equally well to the treatment, depending on the disease progression or the initial severity of the condition. By contrast, some trials do not identify strong differences in efficacy among the different anti-VEGF agents, suggesting that decisions about which therapy to use do not always significantly impact the clinical outcomes.

Often, real world evidence, such as in the InSight study, tends to not report quite as impressive a performance as a clinical trial. The causes of this discrepancy might be patient adherence, differences in treatment protocol, and a difference in injection rate. For example, as we know, in real world data optimal dosing can not be reached and may slightly attenuate real world expected improvements in both visual acuity and retinal anatomy.

On the safety side, many studies have contributed to finding multiple anti-VEGF therapies have a generally good safety profile with infrequent serious adverse events, such as endophthalmitis and thromboembolism. The data presented in this review are consistent with this: adverse events were minimal. In studies, transient increases in intraocular pressure and, rarely, other ocular side effects are reported infrequently and are manageable; this supports the safety of these therapies.

But long term outcomes are a common problem seen in trials. Despite this, anti-VEGF therapy has been shown to maintain benefits over several years, with many studies indicating that patient adherence and recurrence of disease remain major issues. In long term follow-up studies some patients experience the development of decreased visual acuity or increased macular edema during prolonged breakup of treatment or discontinuation. As a result, long term visual improvement maintenance while balancing the treatment burden continues to be a challenge in both clinical trial and real world settings.

Finally, all results from this review are in line with those from other major trials and studies as the efficacy, safety, and long term benefits of anti-VEGF therapy on DR and DME are shown. Nevertheless, patient specific responses, adhesion and disease recurrence has been identified as barriers for flexible dosing strategies as well as personalised treatment plans to achieve better long term outcomes. Further work is needed to better understand such variables and to improve the treatment of diabetic retinal diseases.

Limitations and Implication for Future Research

This review and the studies reviewed were limited by variability between clinical trials and real-world settings in treatment regimen and outcomes. Despite the consistent results of randomized controlled trials of anti–VEGF therapy, real world evidence tends to show less significant improvements of visual acuity and central macular thickness due to uncontrolled factors such as patient nonadherence and treatment nonconsistency. On the clinical side, the long term benefits of anti-VEGF therapy can also be impacted by disease recurrence and the difficulties with taking frequent injections for long term treatment. Future research will continue to address these issues through more flexible, patient specific dosing schedules based on patient adherence and response. Additionally, further research into combination therapies, using anti-VEGF agents along with other interventions including corticosteroids or laser treatment, should assist in optimizing outcomes and gaining maximum benefit from a limited injections and of associated burdens.

Moreover, the general safety profile of anti-VEGF agents shows generally favorable safety profile, but long term studies of potential systemic effects are required. The well documented ocular adverse event of increased intraocular pressure and rare cases of endophthalmitis notwithstanding, the systemic agenda of cardiovascular events is given little attention in a risk balance. Additionally, the lack of well established biomarkers limits the ability to personalise therapies. This type of research could help create more personalized treatment plans – and identify just who will also be the most benefited from certain therapies. From these, future studies can further approach anti-VEGF treatment for diabetic retinopathy and macular edema via a more comprehensive approach to result both in terms of short and long term outcomes for the patients.

CONCLUSION

Overall anti-VEGF therapy is effective at treating diabetic retinopathy and DME, with a high efficacy on visual acuity and retinal anatomy. Long term data buttresses the known benefits of anti-VEGF agents, which includes ranibizumab, aflibercept and bevacizumab over traditional therapies. Long term outcomes are a challenge though because of patient adherence, frequent injections, and risk of disease recurrence. Its favorable safety profile is offset, in part, by the potential for rare but serious adverse events, both ocular and systemic, for which further monitoring and efforts to minimize any risks are warranted. This accumulating evidence, including evidence of improved balance between efficacy and treatment burden with individualized treatment regimens and innovative dosing strategies, indicates that future improvements could be made. Future research should focus on refining anti-VEGF therapy by looking at new ways of personalized medicine, detecting biomarkers to predict treatment response, or indeed looking at less frequent injection schedules or combination therapy. Long term safety studies also need to assess the systemic risks of anti-VEGF therapy, to better guide patient management strategies. Closing these gaps can help future studies lead to more effective, individualized treatments, better patient outcomes and better quality of life for people with diabetic retinopathy and diabetic macular edema.

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