REVIEW

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# Optimizing intravitreal corticosteroid therapy in diabetic macular edema: A review of clinical outcomes, safety considerations, and burden reduction

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## ABSTRACT

**Background:** Diabetic Macular Edema (DME) is a major cause of vision impairment. A significant challenge is the management of patients who are inadequate responders to anti-vascular endothelial growth factor (VEGF) therapy and in addressing the significant treatment burden associated with frequent injections. This review aims to evaluate the efficacy, safety, and ability to reduce treatment burden offered by intravitreal corticosteroids for DME.

**Methods:** A narrative literature review was conducted using PubMed, Google Scholar, and ScienceDirect (2015–2025), focusing on studies reporting best-corrected visual acuity (BCVA), central macular thickness (CMT), intraocular pressure (IOP) elevation, cataract progression, injection frequency, and patient selection criteria. Inclusion emphasized randomized trials, large cohorts, and meta-analyses.

**Results:** DEX implants yield rapid improvements in BCVA and CMT, particularly perioperatively in cataract cases. FA implants demonstrate sustained efficacy over three years, reducing injection frequency by up to 80%. Safety concerns include predictable IOP elevation and cataractogenesis, manageable with monitoring and stratified patient selection. Corticosteroids are especially beneficial for pseudophakic, vitrectomized eyes and anti-VEGF non-responders.

**Conclusion:** Intravitreal corticosteroids represent a viable alternative or adjunct to anti-VEGF therapy, offering durable anatomical and functional benefits while reducing treatment burden. Strategic patient selection and proactive safety monitoring are essential to optimize outcomes.

**Keywords:** Clinical outcome, diabetic macular edema, intravitreal corticosteroids, safety profile, treatment burden.
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## INTRODUCTION

Diabetic Macular Edema (DME) is a leading cause of vision impairment among individuals with diabetes and represents a major complication of diabetic retinopathy. It is estimated that approximately 25–30% of diabetic patients will develop DME during their lifetime. The pathophysiology of DME involves chronic hyperglycemia-induced oxidative stress, inflammation, and vascular endothelial growth factor (VEGF) activation, which disrupts the blood-retinal barrier and leads to fluid accumulation in the macula.[1]

While anti-VEGF therapy remains the first-line treatment, intravitreal corticosteroids such as triamcinolone acetonide (TA), dexamethasone (DEX), and fluocinolone acetonide (FA) have emerged as valuable alternatives, particularly for patients who are non-responsive to anti-VEGF agents or have contraindications. Corticosteroids exert their therapeutic effects by suppressing inflammation and reducing vascular permeability, thereby improving macular thickness and visual acuity. Intravitreal corticosteroids significantly improve best-corrected visual acuity (BCVA) and reduce central macular thickness (CMT), with varying efficacy depending on the type and dosage of the steroid. Notably, the DEX implant showed superior short-term outcomes over anti-VEGF agents in patients with severe DME.[2]

However, corticosteroid therapy is not without risks. Adverse effects such as elevated intraocular pressure (IOP) and cataract formation are critical considerations in treatment planning. Therefore, optimizing intravitreal corticosteroid therapy involves not only maximizing clinical efficacy but also minimizing safety risks and reducing treatment burden, such as injection frequency and clinic visits.[3] Given the rising global prevalence of diabetes and the economic burden associated with DME, there is an urgent need for therapeutic strategies that are effective, safe, and sustainable. This literature review aims to evaluate the clinical outcomes, safety profiles, and burden-reduction strategies of intravitreal corticosteroid therapy in DME, providing evidence-based insights to guide clinical decision-making.

## METHODS

### Search Strategy

A comprehensive literature search was conducted across electronic databases, including PubMed, Google Scholar, and ScienceDirect, for articles published between 2015 and 2025. The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms such as "diabetic macular edema," "DME," "intravitreal corticosteroid," "dexamethasone implant," "fluocinolone acetonide implant," "Ozurdex," "Iluvien," "safety," "intraocular pressure," "treatment burden," and "patient selection." These terms were strategically combined using Boolean operators ("AND" and "OR") to maximize retrieval of relevant studies.

### Inclusion and Exclusion Criteria

The review included clinical studies involving adult patients diagnosed with diabetic macular edema (DME) who were treated with intravitreal corticosteroids, specifically triamcinolone acetonide, dexamethasone implant, or fluocinolone acetonide implant. Included studies were required to report data on at least one of the following outcomes: best-corrected visual acuity (BCVA), central macular thickness (CMT), intraocular pressure (IOP) elevation, cataract progression, endophthalmitis rates, injection frequency, or patient selection criteria. Priority was given to randomized controlled trials, large cohort studies, and systematic reviews with meta-analyses. Exclusion criteria encompassed non-human studies, editorials, conference abstracts, non-peer-reviewed publications, and articles not available in English.

### Data Extraction and Synthesis

Data from eligible studies were systematically extracted, focusing on study design, patient characteristics, intervention details, and relevant outcome measures. The findings were qualitatively synthesized to critically appraise the evidence. The analysis was structured around key themes, including clinical efficacy, safety profiles, treatment burden reduction, and patient stratification strategies. The synthesis aimed to evaluate the risk-benefit ratio of intravitreal corticosteroid therapy and identify optimal candidate profiles for this treatment approach.

## RESULTS AND DISCUSSION

To provide a concise overview of the current evidence and key considerations, a visual summary is presented below as an introduction to the following results and discussion (**Figure 1**).

### Functional and Anatomical Outcomes

The compiled evidence demonstrates that intravitreal corticosteroid therapy produces significant functional and anatomical improvements in DME. Studies focusing on the dexamethasone implant consistently report substantial gains in BCVA, particularly in the peri-operative setting of cataract surgery.[4] Studies have documented significant BCVA improvements alongside substantial decreases in CMT following cataract surgery. These visual acuity gains have been quantified at approximately 15-20 letters on the ETDRS chart, with corresponding reductions in CMT.[5] The strategic value of preoperative implantation has been further validated by research showing an average BCVA gain of 15-18 letters with notable CMT reductions, establishing corticosteroids as a viable pre-cataract surgical approach in complex DME cases.[6] For long-term management, the fluocinolone acetonide implant demonstrates sustained efficacy. Studies have reported maintained BCVA improvements for extended periods, with stable visual acuity outcomes documented for up to three years. This sustained drug delivery mechanism addresses the challenge of chronic DME where other treatments may fail, particularly through its continuous control of inflammation and fluid accumulation in the macula.[7]

### *Mechanistic Basis for Efficacy*

The therapeutic effectiveness of intravitreal corticosteroids is fundamentally rooted in their targeted mechanism of action against the inflammatory components of DME pathogenesis. Research has emphasized that inflammatory mediators play a crucial role in the development of cystoid macular edema, and corticosteroids specifically address this localized inflammation. This mechanistic rationale explains the consistent reductions in CMT and improvements in BCVA observed across studies, particularly in cases where inflammation is a predominant driver of pathology. The anti-inflammatory action provides a distinct therapeutic advantage that complements the mechanisms of other available treatments.[8]

### *Role in Treatment-Resistant and Complex Cases*

Intravitreal corticosteroids demonstrate particular effectiveness in management-resistant scenarios and specific patient populations. For patients with systemic contraindications to anti-VEGF therapy, research has demonstrated the utility of

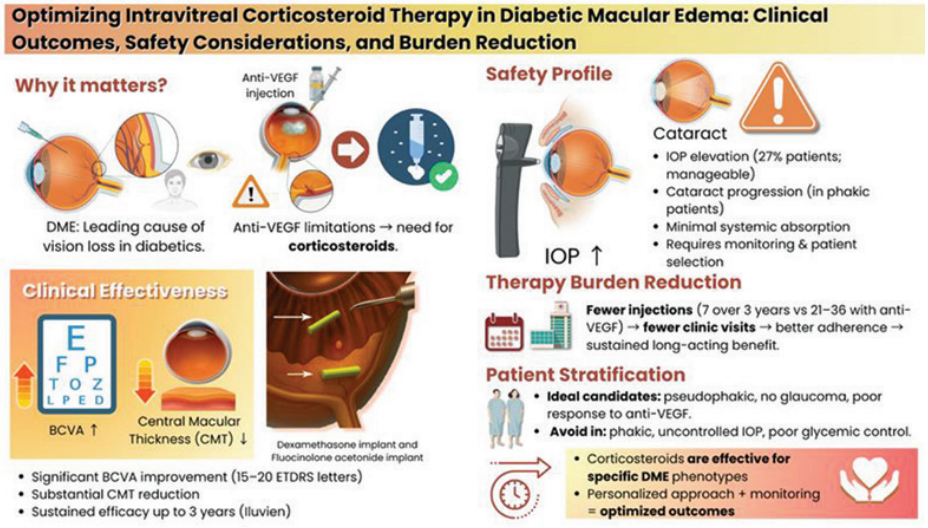


**Figure 1.** Summary of Findings[1,3,5,6,17,18,22,23,30,33,37,38]

intravitreal dexamethasone implants as a primary treatment option in treatment-naive DME patients.[9] In cases of persistent DME despite anti-VEGF treatment, randomized controlled trials have shown that adding a dexamethasone implant to existing ranibizumab therapy enhanced mean visual acuity and produced further reductions in retinal thickness.[10] The value of corticosteroid therapy in refractory DME is further supported by real-world evidence. Clinical studies have highlighted that patients with previously unsuccessful treatments achieved significant improvements in both BCVA and CMT following dexamethasone implantation. Furthermore, research suggests that fluocinolone acetonide can be effectively integrated with anti-VEGF therapies, creating a dual approach that enhances visual outcomes.[11]

### ***Comparative Effectiveness and Clinical Positioning***

Comparative analyses support the strategic positioning of corticosteroids within the DME treatment algorithm. Systematic reviews have indicated that corticosteroids are effective in managing DME with particular advantages in certain patient populations. Further research has reviewed the benefits of switching from anti-VEGF therapy to intravitreal dexamethasone implants, emphasizing improved clinical outcomes through individualized treatment strategies.[12] The relevance of corticosteroid-based interventions persists even with the emergence of newer therapies. Recent studies, while reporting favorable outcomes with newer agents, have simultaneously highlighted the ongoing importance of corticosteroid interventions in cases with suboptimal anti-VEGF response. This evidence collectively positions intravitreal corticosteroids as valuable alternatives or adjuncts to anti-VEGF agents, particularly for patients with complex or refractory DME. The integration of intravitreal corticosteroids into treatment algorithms aligns with the broader goal of personalized therapy, requiring consideration of disease severity, response to prior treatments, and systemic contraindications. These agents offer significant benefits in reducing edema and improving visual acuity, especially in cases where anti-VEGF therapy is contraindicated, ineffective, or requires adjunctive use, underscoring the importance of tailored treatment regimens in optimizing patient outcomes.[13]

### Safety Profile of Intravitreal Corticosteroid Therapy in DME

The safety profile of intravitreal corticosteroid therapy for DME is well defined and largely predictable. Local steroid-related adverse events principally cataract progression and IOP elevation dominate the risk landscape, while serious infectious complications such as endophthalmitis remain uncommon. Steroid implants (dexamethasone and fluocinolone acetonide) in patients with chronic or anti-VEGF refractory DME show that a large share of phakic eyes will develop clinically significant cataract that frequently requires surgical extraction, and that a meaningful minority of treated eyes experience clinically relevant IOP increases that typically respond to topical therapy but occasionally require procedural or surgical glaucoma management.[2,14–16]

Quantitatively, pivotal and real-world studies give a helpful sense of magnitude. In the Macular Edema Assessment of Implantable Dexamethasone (MEAD) program for the 0.7 mg dexamethasone implant, the cumulative rate of cataract surgery in phakic eyes was reported in the high-50s percent range over 3 years, and many real-world series report repeated transient IOP spikes after each treatment cycle (with proportions varying by cohort and IOP threshold). Long-acting fluocinolone acetonide implants (ILUVIEN/0.19–0.2 µg/day formulations) are associated with even higher long-term cataract incidence (most phakic patients develop lens opacity over 2–3 years in pivotal trials) and higher cumulative use of IOP-lowering medications. However, the absolute rate of incisional glaucoma surgery remains comparatively low in many registries. Endophthalmitis after steroid implantation is rare in clinical practice but present in trial reports and therefore remains a required counselling point and justification for meticulous aseptic technique.[17,18]

Clinically, these safety data translate into three practical imperatives: (1) careful patient selection steroids are often reserved for eyes with chronic or anti-VEGF non-response, for patients who would benefit from fewer clinic visits, or when the fellow eye status/lens status makes cataract risk acceptable; (2) standardized baseline and follow-up monitoring (documented lens status, routine IOP checks soon after injection and at regular intervals, and prompt escalation to topical glaucoma therapy or glaucoma specialist input when pressures rise); and (3) informed consent that explains the high likelihood of cataract progression in phakic eyes and the measurable chance of IOP elevation, balanced against the therapy's potential to restore or preserve vision and reduce treatment burden.[19,20]

### Therapeutic Burden Reduction: A Paradigm Shift in DME Management

A critical dimension in optimizing intravitreal corticosteroid therapy for DME is its profound impact on reducing the therapeutic burden. A composite of treatment frequency, logistical challenges, and associated costs for both the patient and the healthcare system. Corticosteroids, particularly in the form of sustained-release implants such as fluocinolone acetonide (ILUVIEN), play a crucial role in alleviating this burden by fundamentally altering the treatment paradigm from one of frequent retreatment to one of sustained management, providing a compelling option for patients with persistent disease unresponsive to conventional therapies.

### ***Quantifying the Reduction in Injection Frequency and Clinic Visits***

The most direct measure of burden reduction is the decrease in required injections and associated clinic visits. This advantage is rooted in the pharmacokinetics of sustained-release implants. One of the principal advantages of using ILUVIEN is its prolonged release profile, with the implant providing continuous delivery of 0.2 µg/day of fluocinolone acetonide for up to three years.[21] This sustained mechanism contrasts sharply with the rapid clearance of anti-VEGF agents, which typically necessitate monthly injections during the initial phase and bi-monthly injections indefinitely for maintenance.

The quantitative difference is substantial. For instance, studies have demonstrated that patients receiving the

fluocinolone implant require significantly fewer clinic visits (an average of 7 over three years) compared to 21-36 visits for those undergoing regular anti-VEGF treatments.[22,23] This represents a 67-81% reduction in appointment frequency. The significant reduction in treatment frequency facilitates better patient adherence and reduces the logistical burdens that come with frequent healthcare visits, which is especially beneficial for patients with comorbidities or those living in remote areas. For a population often managing multiple diabetic complications, reducing the number of trips to the clinic is not merely a convenience but a significant factor in improving quality of life and overall treatment sustainability. This transformative reduction in treatment frequency is a key reason why these corticosteroids are considered viable alternatives in the comprehensive management of diabetic macular edema.[23]

### *Maintaining Clinical Efficacy with a Simplified Treatment Regimen*

A reduction in burden is only clinically meaningful if it is coupled with sustained efficacy. Evidence confirms that the fluocinolone acetonide implant achieves this balance, ensuring that patients receive timely and effective care without the excessive burden of frequent interventions. Clinical studies, including the pivotal Fluocinolone Acetonide for Macular Edema (FAME) trial, have shown that the use of fluocinolone acetonide implants leads to better visual acuity outcomes and decreased central macular thickness over time.[24,25] The continuous drug delivery helps in addressing the underlying inflammation associated with DME while minimizing the cyclical burden of repeated injections typical of anti-VEGF therapies.[26]

This makes it a particularly valuable option for suboptimal responders to anti-VEGF therapy. For patients who have previously failed to respond adequately to anti-VEGF treatment, switching to fluocinolone can improve both anatomical and functional visual outcomes without the need for an increased treatment frequency.[27] Therefore, the implant effectively breaks the cycle of frequent, ineffective injections, replacing it with a less burdensome and often more effective long-term strategy that maintains effective management of DME.

### *Integrating Safety Management into the Burden Equation*

When discussing burden reduction, the safety profile and its associated management costs must be incorporated into the overall calculus. Although there is a risk of elevated IOP and cataract formation associated with corticosteroids, studies show that many patients tolerate fluocinolone implants well after prior treatments, resulting in minimal significant rises in IOP.[28] The need for IOP-lowering medications or, in rare cases, surgery, adds a layer of management. However, this must be weighed against the avoided burden of dozens of injections and visits.

Therefore, the risk-benefit profile becomes favorable given the substantial reduction in treatment burden and the potential for enhanced visual acuity. This profile is optimized through proactive management. Moreover, a strategy that incorporates regular monitoring and patient education can mitigate the safety risks, further enabling a smoother treatment plan that aligns with long-term patient adherence.[29] The requirement for periodic monitoring for IOP is inherently less frequent and less invasive than the burden of monthly intravitreal injections, solidifying the net benefit in burden reduction and contributing to a favorable risk-benefit profile that supports its role in optimized treatment strategies.

## Patient Stratification: Optimizing Outcomes through Targeted Selection

Specific patient characteristics profoundly influence the efficacy and safety of intravitreal corticosteroid therapy for DME. Therefore, a critical component of optimizing this treatment is meticulous patient stratification, which ensures that the potent anti-inflammatory benefits of corticosteroids are delivered to those who will derive the most significant net benefit, thereby maximizing therapeutic success while mitigating risks.

### *The Anti-VEGF Inadequate Responder and Chronic DME Phenotype*

A primary candidate group for intravitreal corticosteroid therapy consists of patients with chronic DME who exhibit an inadequate response to anti-VEGF therapy. The literature indicates that patient stratification for intravitreal corticosteroid therapy primarily involves identifying individuals who are less likely to respond adequately to first-line treatments such as anti-VEGF agents and who may benefit from corticosteroid intervention. Although anti-VEGF therapy remains the initial approach for centrally involved diabetic macular edema (CI-DMO), a significant subset of patients exhibit insufficient response, necessitating consideration of alternative therapies such as corticosteroids.[30] This aligns with earlier findings that corticosteroids are indicated for these patients as they address the inflammation that persists despite anti-VEGF treatment. Studies have demonstrated that corticosteroids can effectively reduce central macular thickness and improve visual acuity in patients with chronic DME.[27,31] The decision to transition is not arbitrary; it hinges on evaluating the response to anti-VEGF treatment and recognizing when continued therapy may pose risks or limited benefits.[30] This makes corticosteroids a vital second-line option for those who have undergone multiple anti-VEGF injections without significant improvement, offering a viable alternative pathway to visual improvement.[32]

### *The Importance of Ocular Status: Pseudophakia and Vitrectomy*

Lens status is a paramount factor in the risk-benefit calculus for corticosteroid therapy. Patients who are phakic and at risk of cataract progression may require careful consideration before initiating corticosteroid therapy, as intraocular steroids can accelerate lens opacification.[33] Consequently, pseudophakic patients, those who have undergone cataract surgery, are generally more suitable candidates. This group often shows more favorable outcomes with corticosteroids due to typically fewer instances of IOP and the eliminated risk of corticosteroid-induced cataract.[34] Conversely, pseudophakic patients may be more suitable candidates, given the reduced risk of cataract-related complications.[33]

Similarly, patients who have undergone vitrectomy may also respond positively to intravitreal corticosteroids. Vitrectomized

eyes have altered pharmacokinetics, often clearing anti-VEGF agents more rapidly. Recent clinical findings suggest that patients who have undergone vitrectomy may also respond positively to intravitreal corticosteroids like the dexamethasone implant. Vitrectomized eyes often demonstrate different pathophysiological conditions, and corticosteroids can provide significant therapeutic benefits in terms of inflammation control and vision correction.[35,36] The sustained-release mechanism of implants is particularly advantageous in this context, counteracting the accelerated drug clearance.

### *Incorporating Systemic Health and Treatment History*

A holistic view of the patient is essential. Individuals with diabetes and systemic comorbidities (for example, those at high cardiovascular risk) may benefit from corticosteroids, particularly in cases of DME refractory to standard anti-VEGF therapy.[37] Furthermore, a patient's prior exposure to steroids is highly informative for stratification. Patient suitability for corticosteroid therapy is also influenced by prior treatment history. For instance, patients who have previously received intravitreal corticosteroids, such as triamcinolone or dexamethasone implants, are often considered for subsequent corticosteroid-based interventions, especially if they demonstrate persistent or recurrent edema.[38] This prior exposure helps clinicians assess the likelihood of response and potential adverse effects.

### *Mitigating Risk through Proactive Management and Monitoring*

Stratification is not solely about selecting candidates but also about proactive risk management. While corticosteroids are effective, careful monitoring is necessary to manage potential increases in IOP, especially in patients with a history of elevated IOP following previous steroid treatments.[2] The guidelines emphasize that the decision to transition to corticosteroid therapy hinges on evaluating the response to anti-VEGF treatment and recognizing when continued therapy may pose risks or limited benefits, which includes an assessment of the patient's ability to adhere to the necessary follow-up for IOP monitoring.[30] Regular assessments of IOP and visual outcomes are crucial to ensure that treatment remains both safe and effective.[2]

In summary, the suitability of patients for intravitreal corticosteroid therapy depends on various factors, including the duration of DME, previous treatment responses, ocular history, and the presence of systemic comorbidities**.** The overarching goal of patient stratification for intravitreal corticosteroid therapy is to evaluate prior treatment responses, lens status, and risk factors for adverse effects to optimize treatment outcomes while minimizing potential risks, ensuring that corticosteroids are reserved for those most likely to benefit. This tailored approach is fundamental to optimizing intravitreal corticosteroid therapy, ensuring it is deployed strategically within the DME treatment arsenal.

## Study Limitations

The application of intravitreal corticosteroid therapy for DME is constrained by several significant limitations, as evidenced by the literature. These limitations pertain to safety, efficacy, and methodological aspects of clinical studies, which collectively inform critical future research directions.

### *Safety Concerns: Intraocular Pressure Elevation and Cataractogenesis*

A primary limitation is the well-documented risk of adverse events. The most prevalent safety concerns are steroid-induced elevation of IOP and cataract formation. Algorithms have been developed to enable tailored monitoring and to confirm that patients with a higher baseline IOP or a history of ocular hypertension are at increased risk, thereby necessitating vigilant management and potentially leading to treatment discontinuation.[39] Furthermore, cataract progression is a frequent complication that can ultimately impair vision and require surgical intervention, a significant drawback noted in previous studies.[9]

### *Variable and Transient Efficacy*

Corticosteroids are effective in reducing macular edema. However, their therapeutic response is variable and often not sustained in the long term. Evidence from a meta-analysis indicates that corticosteroids may not provide superior or durable visual outcomes compared to anti-VEGF agents.[40] Consequently, repeated injections are frequently required, as reported in case studies, thereby increasing the cumulative risk of adverse effects and the overall treatment burden.[41]

### *Methodological Constraints of Existing Literature*

The body of evidence supporting corticosteroid use has notable methodological weaknesses. A key limitation across numerous clinical trials is the short follow-up duration, often limited to 6-12 months.[42] This is insufficient to fully evaluate the long-term efficacy, safety, and impact on diabetic retinopathy progression.[43] Additionally, many studies are hampered by relatively small sample sizes, which reduces statistical power, increases result variability, and limits the generalizability of findings to broader, more diverse patient populations.[44,45]

## Patient-Specific Factors and Inadequate Demographic Reporting

Patient-specific factors highly influence the effectiveness and safety profile of corticosteroid therapy. Evidence indicates the necessity for individualized treatment regimens, as systemic comorbidities (e.g., cardiovascular or renal disease) and ocular characteristics can significantly affect outcomes. However, many studies fail to account for adequately or report comprehensive demographic and comorbidity data, creating a gap in understanding which patient subpopulations are most suited for this treatment.[46,47]

# CONCLUSION

Optimizing intravitreal corticosteroid therapy for DME requires a comprehensive approach that goes beyond clinical efficacy to address long-term safety and reduce the overall treatment burden for patients. While this therapy has demonstrated significant visual benefits, challenges such as increased intraocular pressure, cataract risk, and the cost of managing side effects remain barriers to widespread adoption. By strengthening the evidence

base through long-term studies, applying personalized treatment strategies, and exploring more efficient combination therapies, intravitreal corticosteroids can become a more targeted and effective option. This approach not only enhances clinical outcomes but also ensures that treatment is safe, sustainable, and capable of alleviating the physical, psychological, and financial burden experienced by DME patients.

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