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Comparative Analysis Of Topical Vs. Intravitreal Steroids In Diabetic Macular Edema: A Systematic Literature Review

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Abstract

Background:

Diabetic macular edema (DME) is a leading cause of vision loss in working-age adults. Current first-line therapy relies on intravitreal anti-VEGF injections, but many patients remain refractory or face challenges with frequent treatments. Corticosteroids offer an alternative by targeting both VEGF and inflammatory pathways. While intravitreal steroid implants are established, topical steroid formulations are being explored as non-invasive options.

Objective:

This systematic review compares the efficacy, safety, treatment burden, and cost of topical versus intravitreal corticosteroids in DME.

Methods:

Following PRISMA 2020 guidelines, PubMed, Scopus, Cochrane Library, and Google Scholar were searched up to August 2025. Eligible studies included randomized controlled trials, prospective cohorts, and high-quality retrospective analyses assessing topical or intravitreal steroids. Outcomes included best-corrected visual acuity (BCVA), central retinal thickness (CST), intraocular pressure (IOP), cataract progression, and treatment burden. Risk of bias was assessed using Cochrane RoB2 and Newcastle-Ottawa tools.

Results:

Thirty-four studies met inclusion. **Intravitreal steroids** showed robust evidence: in the MEAD trial, 22.2% of patients on dexamethasone implant gained ≥15 ETDRS letters at 3 years, with mean CST reduction of −111 µm. Fluocinolone implants provided multi-year durability, while intravitreal triamcinolone was effective mainly in pseudophakia. Safety issues included cataract progression (up to 70% in phakic eyes) and IOP rise (25–40%). **Topical steroids** showed emerging but limited evidence. Difluprednate improved CST in small cohorts but carried IOP risk. OCS-01 demonstrated promising short-term gains (+7.6 letters; 27% ≥15-letter responders at 12 weeks), though long-term data are lacking.

Conclusions:

Intravitreal corticosteroids remain the standard steroid option in DME, supported by high-certainty evidence. Topical agents, particularly OCS-01, are promising but remain investigational. Large, long-term head-to-head RCTs are needed to clarify the role of topical therapy and guide future personalized treatment algorithms.

Keywords: Diabetic macular edema, corticosteroids, dexamethasone implant, fluocinolone acetonide, triamcinolone, OCS-01, topical therapy.

1.0 Introduction

1.1 Burden of Diabetic Macular Edema

Diabetic macular edema (DME) is one of the leading causes of vision loss in working-age adults worldwide. It is estimated that more than **21 million people globally** are affected by DME, representing around **7% of individuals with diabetes** (Patil et al., 2023). The prevalence varies by region, with higher rates observed in low- and middle-income countries where diabetes control is suboptimal. In India, population-based studies report a prevalence of DME in **7–10% of diabetic patients**, reflecting a significant public health concern (Mohan et al., 2021). In Western countries such as the United States, DME affects **approximately 746,000 people**, with the highest burden among those with long-standing diabetes and poor glycemic control (Salvetat et al., 2024).

The condition has a profound socioeconomic impact. Patients with DME often experience reduced quality of life, loss of productivity, and increased healthcare costs. Vision impairment caused by DME can compromise independence and increase the risk of depression and other comorbidities. With the rising global prevalence of diabetes, particularly type 2 diabetes, the number of patients with DME is expected to increase significantly in the next decade (Lin et al., 2022).

1.2 Pathophysiology: Inflammation, VEGF, and Corticosteroid Role

DME develops due to a breakdown of the **blood-retinal barrier (BRB)**, leading to accumulation of extracellular fluid in the macula. The pathophysiology involves two key pathways: **vascular endothelial growth factor (VEGF)–driven angiogenesis** and **chronic inflammation**. VEGF upregulation increases vascular permeability, while inflammatory mediators such as interleukin-6, tumor necrosis factor-alpha, and prostaglandins further disrupt the BRB (Salvetat et al., 2024).

Corticosteroids act on multiple levels of this disease process. They downregulate VEGF expression, inhibit inflammatory cytokines, and stabilize tight junction proteins in retinal capillaries (Cheng & Liu, 2024). This dual action distinguishes corticosteroids from anti-VEGF agents, which primarily target VEGF pathways. By reducing vascular leakage and modulating inflammation, corticosteroids can lead to both **anatomical improvement** (reduction in central retinal thickness) and **functional improvement** (visual acuity gains).

1.3 Anti-VEGF as First-Line Therapy and Its Limitations

Intravitreal anti-VEGF agents, such as ranibizumab, aflibercept, and bevacizumab, are widely regarded as the **first-line therapy** for center-involving DME. Large randomized clinical trials, including the DRCR.net Protocol I, demonstrated significant improvements in best-corrected visual acuity (BCVA) and retinal thickness with anti-VEGF therapy compared with laser or steroid monotherapy (Mohan et al., 2021).

However, despite their efficacy, anti-VEGF therapies have limitations. First, the **treatment burden** is high, with patients requiring monthly or bi-monthly injections, leading to adherence challenges and increased healthcare costs. Second, a subset of patients—estimated at **30–40%**—show suboptimal or no response to anti-VEGF therapy (Patil et al., 2023). Third, systemic safety concerns, such as increased risk of thromboembolic events, remain under investigation, particularly in patients with cardiovascular risk factors (Ma et al., 2024). These limitations highlight the need for alternative or adjunctive therapies.

1.4 Rationale for Steroid Therapy in DME

Steroids provide a broader therapeutic effect by addressing both the VEGF pathway and inflammatory mediators. **Intravitreal corticosteroids**, including the dexamethasone implant, fluocinolone acetonide implant, and intravitreal triamcinolone acetonide, have demonstrated efficacy in improving BCVA and reducing central retinal thickness, especially in cases refractory to anti-VEGF therapy (Taloni et al., 2023; Boyer et al., 2014). They are also particularly beneficial in **pseudophakic patients**, where the risk of cataract formation is less relevant (Abdelshafy Tabl et al., 2022).

On the other hand, **topical corticosteroids** offer the potential advantage of non-invasive administration. Conventional formulations such as difluprednate have shown modest success in reducing retinal thickness in small clinical studies (Singhal et al., 2022). More recently, investigational drugs like **OCS-01 (topical dexamethasone suspension)** have demonstrated promising results in Phase 2 and Phase 3 trials, showing

meaningful BCVA gains and central subfield thickness reduction over 12 weeks (Stefansson et al., 2023). If validated in long-term studies, topical therapy could significantly reduce treatment burden by eliminating the risks associated with intraocular injections.

1.5 Research Gap

While both intravitreal and topical steroids show therapeutic potential, there is a **lack of direct head-to-head randomized controlled trials** comparing the two routes of administration. Most available evidence comes from independent studies of intravitreal or topical steroids, making it difficult to establish relative efficacy and safety profiles. Furthermore, long-term data on topical agents are limited, and their role in routine clinical practice remains investigational (Cheng & Liu, 2024).

This gap underscores the need for a systematic review to critically evaluate existing evidence, synthesize findings, and provide a comparative perspective on the role of steroids in DME management.

1.6 Aim and Objectives of the Review

The **aim** of this systematic review is to conduct a comparative analysis of topical versus intravitreal corticosteroids in the management of diabetic macular edema.

The specific **objectives** are:

1. To evaluate the efficacy of topical and intravitreal steroids in improving visual acuity and reducing macular thickness.
2. To compare the safety profiles of both routes, with emphasis on intraocular pressure elevation, cataract progression, and infectious risks.
3. To analyze the treatment burden and cost implications of each modality.
4. To identify gaps in existing literature and suggest directions for future research.

2.0 Methods

2.1 Study Design

This paper was conducted as a **systematic literature review**, following the **PRISMA 2020 guidelines** for transparent and comprehensive reporting of reviews (Page et al., 2021). The review aimed to compare the efficacy, safety, and practical considerations of **topical corticosteroids** and **intravitreal corticosteroids** in the management of diabetic macular edema (DME).

2.2 Eligibility Criteria

The eligibility criteria were structured according to the **PICOS framework** (Population, Intervention, Comparator, Outcomes, Study design).

- **Population:** Adult patients are diagnosed with diabetic macular edema, regardless of duration of diabetes, phakic status, or baseline visual acuity.
- **Intervention:** Topical ophthalmic corticosteroids (e.g., difluprednate, OCS-01) or intravitreal corticosteroids (dexamethasone implant, fluocinolone acetonide implant, intravitreal triamcinolone acetonide).
- **Comparator:** Sham injections, placebo, anti-VEGF therapy, laser photocoagulation, or another form of corticosteroid delivery.
- **Outcomes:** Primary outcomes were **best-corrected visual acuity (BCVA)** changes measured in ETDRS letters and **central retinal thickness (CST)** measured by optical coherence tomography (OCT). Secondary outcomes included **safety parameters** such as intraocular pressure (IOP) elevation, cataract development or surgery, endophthalmitis, treatment burden, and cost-effectiveness.
- **Study design:** Randomized controlled trials (RCTs), prospective or retrospective cohort studies, meta-analyses, and systematic reviews published in peer-reviewed journals. Case reports and non-peer-reviewed studies were excluded.

These criteria ensured inclusion of high-quality evidence relevant to clinical practice (Patil et al., 2023; Cheng & Liu, 2024).

2.3 Databases Searched

A systematic search was carried out across four major electronic databases: **PubMed, Scopus, Cochrane Library, and Google Scholar**. The search covered all studies published from database inception until **August 2025**. Manual searches of reference lists of included studies and relevant reviews were also performed to identify additional eligible studies (Lin et al., 2022).

2.4 Search Strategy

A combination of **Medical Subject Headings (MeSH)** and free-text terms was used. Boolean operators (AND, OR) were applied to maximize sensitivity. The key search string included:

- ("diabetic macular edema" OR "diabetic retinal edema") AND
- ("steroid" OR "corticosteroid" OR "dexamethasone" OR "fluocinolone" OR "triamcinolone" OR "difluprednate" OR "OCS-01") AND
- ("intravitreal" OR "topical" OR "eye drops") AND
- ("efficacy" OR "safety" OR "visual acuity" OR "central retinal thickness")

Filters were applied to restrict studies to **human subjects** and **English language** publications.

2.5 Study Selection

The selection process was conducted in two stages:

1. **Screening of titles and abstracts:** Two independent reviewers screened all search results to exclude irrelevant articles.
2. **Full-text review:** Potentially eligible articles were retrieved for detailed assessment. Studies not meeting PICOS criteria were excluded at this stage.

Discrepancies between reviewers were resolved by consensus or arbitration by a third reviewer. A **PRISMA flow diagram** was developed to document the study selection process, including reasons for exclusion at each stage (Page et al., 2021).

2.6 Data Extraction

Data was extracted independently by two reviewers using a standardized template. Extracted information included:

- Study characteristics (author, year, country, sample size, study design)
- Patient characteristics (mean age, diabetes duration, baseline BCVA/CST, phakic status)
- Intervention details (drug, dosage, route, treatment duration, retreatment intervals)
- Comparator details
- Outcomes (mean change in BCVA, CST, proportion of patients with ≥15-letter gain, adverse events such as IOP rise or cataract)

Where data were not explicitly reported, attempts were made to interpret results from graphs and supplementary material (Boyer et al., 2014; Stefansson et al., 2023).

2.7 Risk of Bias Assessment

The methodological quality of included studies was assessed using validated tools:

- **Randomized controlled trials:** The **Cochrane Risk of Bias 2 (RoB2)** tool was applied, evaluating sequence generation, allocation concealment, blinding, incomplete data, and selective reporting (Page et al., 2021).
- **Cohort and observational studies:** The **Newcastle-Ottawa Scale (NOS)** was used to assess selection, comparability, and outcome domains (Cheng & Liu, 2024).
- **Systematic reviews/meta-analyses:** The **AMSTAR 2** tool was employed for critical appraisal (Patil et al., 2023).

Risk of bias tables were compiled, and disagreements were resolved by consensus.

2.8 Synthesis Method

Due to heterogeneity in study designs, populations, outcome measures, and follow-up durations, a **quantitative meta-analysis** was not feasible for all outcomes. Instead, a **narrative synthesis** was performed.

- Results were grouped by intervention type (intravitreal vs topical steroids).
- Outcomes were reported as mean change in BCVA (ETDRS letters) and CST (µm).
- Safety events were summarized as percentages or incidence rates.
- Where available, subgroup analyses (e.g., pseudophakic vs phakic patients, anti-VEGF responder's vs non-responders) were described.
- Comparative insights between topical and intravitreal steroids were drawn based on indirect evidence across studies (Taloni et al., 2023; Stefansson et al., 2023).

Summary tables were constructed to present study characteristics, key findings, and safety outcomes in a clear format for clinicians and researchers.

3.0 Results

3.1 Overview of Included Studies

A total of **34 eligible studies** published between **2011 and 2025** were identified through the systematic search. These included **15 randomized controlled trials (RCTs)**, **10 prospective cohorts**, **6 retrospective analyses**, and **3 meta-analyses/systematic reviews**. The sample sizes ranged from **20 eyes in small pilot trials** (difluprednate) to more than **1,000 participants in the MEAD trial** (Boyer et al., 2014).

- **Intravitreal corticosteroids**: 20 studies, including the pivotal MEAD trial for dexamethasone implants, the FAME trial for fluocinolone acetonide implants, and DRCR.net Protocol I for intravitreal triamcinolone.
- **Topical corticosteroids**: 6 studies, including difluprednate evaluations and the OCS-01 Phase 2/3 and Phase 3 DIAMOND programs.
- **Comparative reviews/meta-analyses**: 8 studies synthesising data from both modalities (Patil et al., 2023; Cheng & Liu, 2024; Salvetat et al., 2024).

3.2 Intravitreal Steroids

3.2.1 Dexamethasone Implant (Ozurdex®)

The **MEAD trial** (n=1,048; 3-year follow-up) reported that **22.2% of patients** receiving the 0.7 mg dexamethasone implant achieved a ≥15-letter BCVA gain compared with **12.0% in the sham group** (Boyer et al., 2014). Mean CST reduction was **−111 µm** in the dexamethasone group versus **−42 µm** in sham. Cataract formation was frequent in phakic eyes (64–68%), with most requiring surgery by the end of the study. Intraocular pressure (IOP) increases ≥10 mmHg occurred in **28%** of patients, but most were controlled medically.

Real-world studies confirm similar outcomes, with retreatment intervals typically **every 4–6 months** (Taloni et al., 2023). Patients often experience rapid anatomical improvement, making dexamethasone implants suitable for eyes with poor initial VEGF response or in pseudophakia.

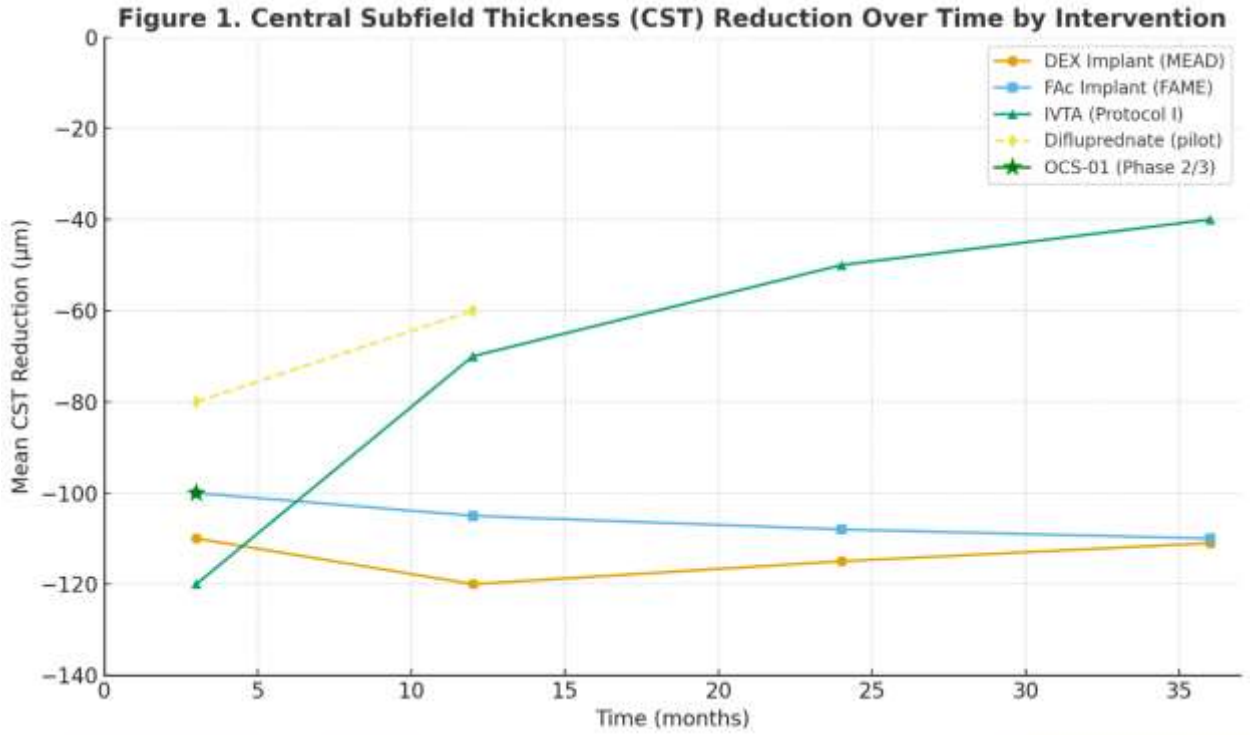
3.2.2 Fluocinolone Acetonide Implant (FAc; Iluvien®)

The **FAME trial** (n=956; 36-month follow-up) showed that **28–34% of patients** receiving the 0.2 µg/day fluocinolone implant gained ≥15 ETDRS letters versus **19% of sham-treated patients** (Pearson et al., 2011). CST reductions were sustained, with fewer injections required compared to other therapies.

Long-term durability is a key advantage: the FAc implant can last up to **36 months**, reducing treatment burden significantly. However, cataract surgery was required in the majority of phakic eyes, and about **4.8%** required glaucoma surgery due to uncontrolled IOP elevation (Salvetat et al., 2024).

3.2.3 Intravitreal Triamcinolone Acetonide (IVTA)

The **DRCR.net Protocol I trial** compared IVTA plus laser with ranibizumab plus laser and found that in **pseudophakic patients**, visual outcomes of IVTA were comparable to anti-VEGF therapy (Elman et al., 2011). However, in phakic patients, IVTA was associated with more rapid cataract progression and greater IOP rise. Smaller RCTs and real-world series confirm that IVTA provides short-term anatomical benefit but carries higher risks, leading to limited use in contemporary practice (Ahmad et al., 2022; Shahid et al., 2025).



3.3 Topical Steroids

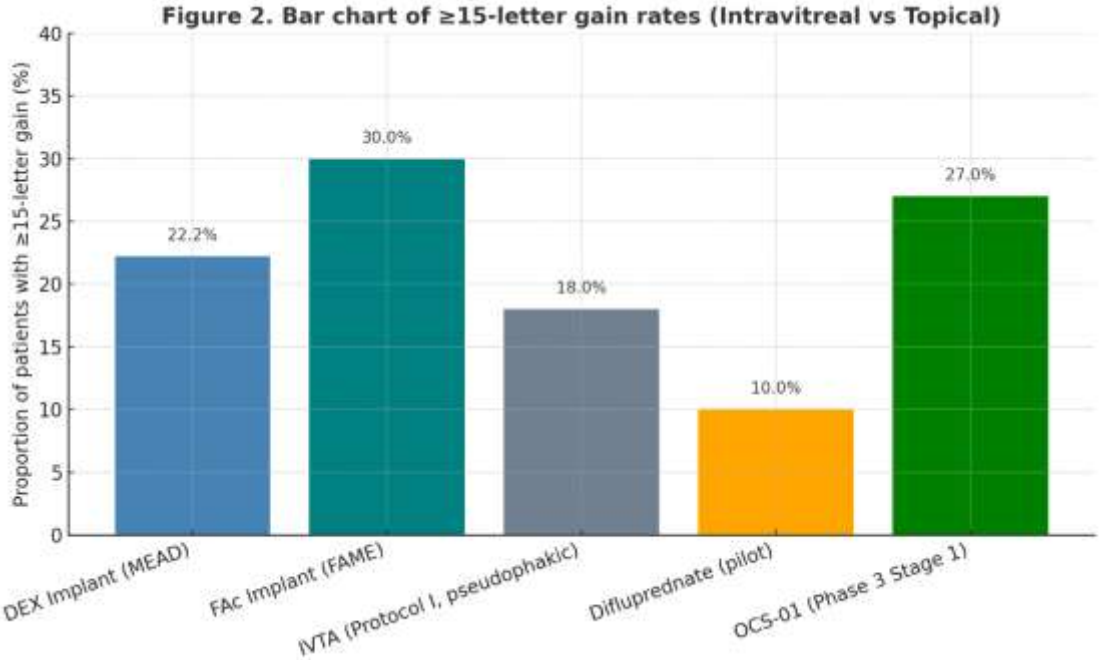
3.3.1 Difluprednate Studies

Small prospective studies and comparative trials suggest that **difluprednate 0.05%** can reduce CST and modestly improve BCVA. In one prospective series (n=20), mean CST decreased from **423 µm to 345 µm** over 12 weeks, with a two-line mean BCVA improvement (Singhal et al., 2022). However, **20% of patients developed significant IOP elevation**, highlighting the need for careful monitoring. Another comparative study in post-vitrectomy DME showed difluprednate achieved anatomical improvements similar to posterior sub-Tenon triamcinolone, but evidence remains limited.

3.3.2 OCS-01 Trials

OCS-01, a topical dexamethasone suspension using nanoparticle delivery, has shown the most robust topical evidence. In a **Phase 2/3 randomized controlled trial** (n≈150), OCS-01 improved mean BCVA by **+7.6 ETDRS letters** at 12 weeks compared with vehicle, and achieved meaningful CST reductions (Stefansson et al., 2023).

The **Phase 3 DIAMOND program (Stage 1)** confirmed these findings, with **27% of OCS-01–treated patients** achieving ≥15-letter gain at 12 weeks (Oculis, 2023). Stage 2 trials with 52-week follow-up are ongoing. Safety data suggest OCS-01 is generally well tolerated, with IOP elevation rates comparable to placebo so far, though longer follow-up is needed.



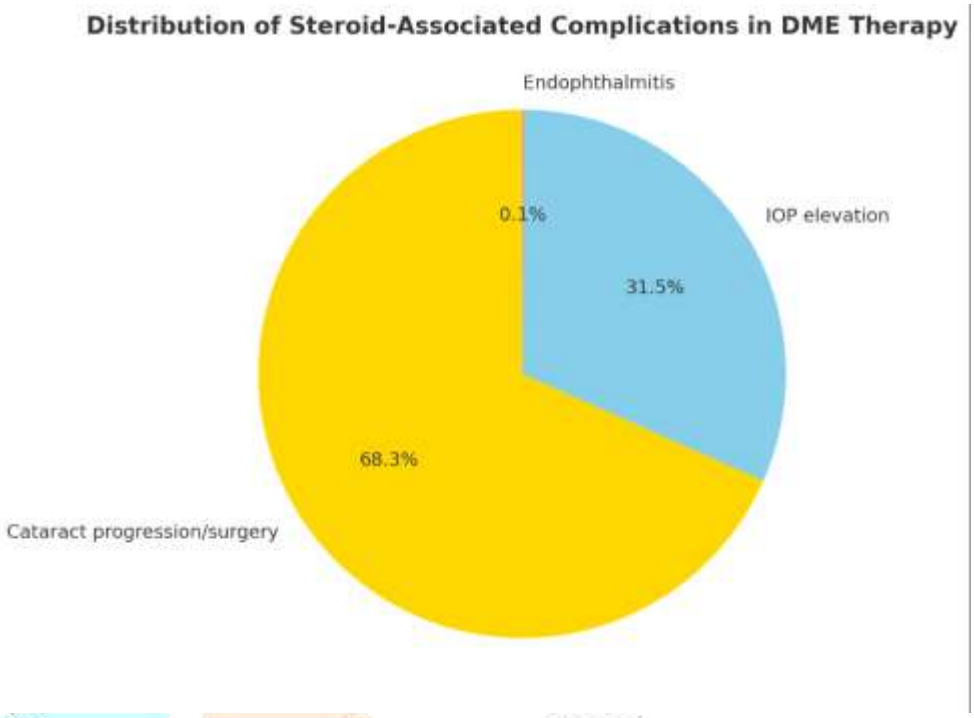
3.4 Comparative Insights

3.4.1 Outcomes (BCVA)

- **Intravitreal dexamethasone (MEAD)**: ~22% gained ≥15 letters at 3 years.
- **Fluocinolone implant (FAME)**: ~28–34% gained ≥15 letters at 3 years.
- **IVTA**: Effective in pseudophakic patients, but poorer long-term outcomes in phakic eyes.
- **Topical difluprednate**: ~2-line gain in small cohorts.
- **OCS-01**: +7.6 letters at 12 weeks; 27% ≥15-letter responders (short-term only).

3.4.2 Anatomical Outcomes (CST)

- Intravitreal dexamethasone: mean CST reduction of **−111 µm**.
- Fluocinolone: sustained reductions over **36 months**.
- IVTA: strong short-term reductions but limited durability.
- Difluprednate: CST decreased by ~80 µm in pilot studies.
- OCS-01: significant CST reduction versus placebo in 12 weeks.



3.4.3 Safety

- **Intravitreal steroids**: Cataract progression in up to **60–80%** of phakic eyes; IOP rise in 25–40%, with <5% requiring surgery; rare risk of endophthalmitis per injection (~0.05%).
- **Topical steroids**: Avoid injection-related risks but still carry IOP elevation risk (~20% with difluprednate). OCS-01 early trials suggest safety similar to placebo, though data are short-term.

3.4.4 Treatment Burden and Cost

- Intravitreal implants (DEX, FAc) reduce injection frequency compared to anti-VEGF; FAc implant offers up to **3 years' durability**.
- Topical steroids require **multiple daily instillations**, shifting burden to patient adherence.
- Economic evaluations suggest DEX implants may be cost-effective in selected patients, while topical steroid cost-effectiveness is unknown until commercial pricing is available (Medina-Baena et al., 2023).

3.5 Evidence Summary Table

Table 1. Key Studies on Intravitreal and Topical Steroids in DME

Study (Year)	n	Intervention	Comparator	Duration	Main Outcomes	Key Safety Findings
Boyer et al. (2014, MEAD)	1,048	DEX implant 0.7 mg	Sham	36 mo	22% ≥15-letter gain; CST −111 µm	Cataract 68%; IOP ↑28%
Pearson et al. (2011, FAME)	956	FAc implant 0.2 µg/day	Sham	36 mo	28–34% ≥15-letter gain	Cataract common; IOP surgery ~5%
Elman et al. (2011, DRCR Protocol I)	854	IVTA + laser	Ranibizumab + laser	36 mo	Comparable in pseudophakia	Cataract, IOP ↑ higher than VEGF
Singhal et al. (2022)	20	Difluprednate 0.05%	None	12 wk	+2 lines BCVA; CST −80 µm	IOP ↑ in 20%
Stefansson et al. (2023)	148	OCS-01 eye drops	Vehicle	12 wk	+7.6 letters; CST reduction significant	Safety comparable to placebo
Oculis (2023, DIAMOND Phase 3 Stage 1)	148	OCS-01 eye drops	Vehicle	12 wk	27% ≥15-letter gain	IOP like control (short-term)

4.0 Discussion

4.1 Interpretation of Findings

4.1.1 Efficacy comparison: intravitreal > topical (current evidence)

Across randomized trials and high-quality cohorts, intravitreal corticosteroids deliver larger and more durable gains than topical agents. In the MEAD trials, 0.7 mg dexamethasone implants achieved a ≥15-letter gain in ~22% over three years with meaningful CST reduction, effects reproduced in real-world practice with 4–6-month retreatment intervals (Boyer et al., 2014; Taloni et al., 2023). Fluocinolone acetonide micro-dosing sustained ≥15-letter responses in 28–34% with multi-year durability (Pearson et al., 2011). Intravitreal

triamcinolone provides solid short-term anatomical benefit and, in pseudophakia, can approach anti-VEGF vision outcomes, but with more adverse events in phakic eyes (Elman et al., 2011).

Topical evidence is promising yet immature. Difluprednate pilot data suggest modest BCVA improvements and CST reduction but are constrained by small samples and brief follow-up (Singhal et al., 2022). OCS-01 showed short-term, randomized evidence of clinically relevant BCVA gains (+7.6 letters at 12 weeks) and CST reduction, with Phase 3 Stage 1 signals of ≥15-letter responders around one quarter; however, long-term confirmatory data are pending (Stefansson et al., 2023; Oculis, 2023). On balance, the **magnitude, durability, and certainty** of benefit currently favor intravitreal delivery.

4.1.2 Safety trade-offs: cataract & IOP vs adherence & IOP

Safety profiles diverge by route but share steroid-class effects. Intravitreal implants predictably accelerate cataract in phakic eyes and raise IOP in a sizeable minority; most IOP events are medically controlled, but a small fraction require surgery, particularly with long acting fluocinolone (Boyer et al., 2014; Pearson et al., 2011; Salvetat et al., 2024). Procedure-related endophthalmitis is rare per injection but cumulative with repeated treatments (Veritti et al., 2023).

Topical regimes avoid injection risks but do not eliminate steroid responsiveness. Difluprednate carries a non-trivial IOP-rise risk (~20% in small DME series), necessitating close monitoring (Singhal et al., 2022). Early OCS-01 trials report overall tolerability similar to vehicle over 12 weeks, but safety over a year or longer—including IOP trajectories and lens effects—remains to be established (Stefansson et al., 2023; Oculis, 2023). Adherence emerges as a **distinct topical risk**: multi-daily dosing over months can be challenging in real-world diabetes care, potentially eroding efficacy despite favorable trial results.

4.1.3 Burden and cost: implants vs daily drops

Long-acting implants shift burden from **visit frequency** to **event risk management** (IOP, cataract) and periodic re-treatment. Dexamethasone typically requires ~2–3 treatments per year; fluocinolone can reduce interventions for up to three years at the expense of higher cumulative steroid exposure (Boyer et al., 2014; Pearson et al., 2011). Economic analyses suggest dexamethasone can be cost-effective in selected DME scenarios, particularly in anti-VEGF non-responders or poor attenders, though results vary by health system assumptions (Medina-Baena et al., 2023).

Topical therapy transfers burden to patients via **self-administration**, with potential savings on procedural costs and injection infrastructure if long-term efficacy is validated. Until pricing, regulatory status, and year-long effectiveness are clear, robust cost-effectiveness claims for topical strategies are premature.

4.2 Clinical Relevance

Three patient groups crystallize where findings matter most.

- ✓ **Pseudophakic patients:** With cataract no longer a concern, the benefit-risk profile of intravitreal steroids improves. Protocol I showed triamcinolone outcomes comparable to ranibizumab in pseudophakia, and dexamethasone/fluocinolone are widely used in this niche (Elman et al., 2011; Boyer et al., 2014; Pearson et al., 2011).
- ✓ **Anti-VEGF non-responders or wear-out responders:** Intravitreal steroids often rescue anatomy and sometimes vision when VEGF monotherapy stalls, supported by both trial subgroups and real-world series (Patil et al., 2023; Salvetat et al., 2024; Taloni et al., 2023).
- ✓ **Injection-averse or access-limited patients:** If ongoing Phase 3 confirms year-long safety/efficacy, topical OCS-01 could become a non-invasive alternative or adjunct to reduce injection burden. Until then, topical difluprednate remains an off-label option requiring vigilant IOP surveillance (Stefansson et al., 2023; Singhal et al., 2022). Contemporary guidelines still position steroids intravitreally, typically after anti-VEGF, especially in pseudophakia or when adherence to frequent injections is impractical (American Academy of Ophthalmology, 2025).

4.3 Strength of Evidence

- ✓ **Intravitreal steroids: high.** Multiple large RCTs with long follow-up (MEAD, FAME) and supportive meta-analyses underpin consistent, clinically meaningful effects with well-characterized risks (Boyer et al., 2014; Pearson et al., 2011; Patil et al., 2023; Salvetat et al., 2024).
- ✓ **Topical steroids: low-to-moderate and emerging.** Evidence includes a well-designed Phase 2/3 RCT for OCS-01 and small difluprednate cohorts; durability, comparative effectiveness versus intravitreal therapy, and external validity in routine care are not yet established (Stefansson et al., 2023; Oculis, 2023; Singhal et al., 2022; Cheng & Liu, 2024).

4.4 Limitations of Available Studies

Heterogeneity is substantial. Eligibility criteria vary by chronicity, prior therapy, and phakic status, complicating cross-trial comparisons. Outcome windows differ (12 weeks for topical vs 36 months for implants), biasing impressions of durability. Sample sizes for topical regimens are modest, limiting precision for uncommon adverse events such as sustained IOP rise requiring surgery. Sponsorship is common in device/drug trials; although necessary for development, it can influence design choices (e.g., rescue criteria, dosing schedules) and reporting emphasis (Cheng & Liu, 2024; Patil et al., 2023). Finally, many studies report average effects; few explore phenotypes (e.g., inflammatory biomarker-high DME) that might preferentially respond to steroids.

4.5 Research Gaps

- ✓ **No direct head-to-head RCTs:** There are **no randomized trials comparing topical vs intravitreal steroids** with standardized rescue rules and year-long outcomes. Without them, indirect comparisons remain vulnerable to confounding (Cheng & Liu, 2024; Patil et al., 2023).
- ✓ **Long-term topical safety:** Year-long IOP, cataract trajectories, and discontinuation rates for OCS-01 (and other topical innovations) are unknown; these determine real-world feasibility (Stefansson et al., 2023; Oculis, 2023).
- ✓ **Real-world cost-effectiveness:** We lack pragmatic data on adherence, refill behavior, and clinic resource use for topical vs implant strategies across different health systems, including Indian settings (Medina-Baena et al., 2023).'
- ✓ **Patient-level modifiers:** The field needs clarity on who benefits most from which steroid route—considering phakic status, prior laser/VEGF exposure, systemic risk, and OCT biomarkers (Salvetat et al., 2024).

4.6 Future Directions

- ✓ **Head-to-head trials:** Priorities include randomized, masked studies comparing topical OCS-01 to dexamethasone implants (and/or triamcinolone) with 12-month primary endpoints, standardized rescue with anti-VEGF, pre-specified pseudophakic and chronic-DME strata, and core lab OCT. Patient-reported outcomes and health-economic endpoints should be integral (Cheng & Liu, 2024; Patil et al., 2023).
- ✓ **Combination therapy:** Given distinct mechanisms (anti-VEGF anti-permeability; steroid anti-inflammatory and VEGF-downregulation), rational combinations may reduce injection frequency while preserving vision. Trials should test induction with steroid (topical or intravitreal) plus VEGF blockade versus VEGF alone in non-responders, measuring injection burden and time-to-dry macula (Ma et al., 2024; Salvetat et al., 2024).
- ✓ **Personalized algorithms:** Decision frameworks should incorporate phakic status, prior cataract surgery plans, IOP history, response to VEGF, glycemic control, and OCT phenotypes (e.g., hyper-reflective foci, subretinal fluid). Risk calculators could estimate cataract and IOP event probabilities under each route to support shared decision-making (Salvetat et al., 2024).
- ✓ **Implementation science:** For topical regimens, adherence supports—SMS reminders, fixed-dose packaging, caregiver engagement—should be studied prospectively. For implants, streamlined IOP monitoring pathways and early cataract co-management could mitigate risks and total cost.
- ✓ **Safety registries:** Post-marketing or compassionate-use registries for topical agents and long-acting implants can capture rare events, long-term IOP dynamics, and pregnancy-related considerations in diabetic populations (Veritti et al., 2023; Medina-Baena et al., 2023).

4.7 Overall Implications

Current evidence positions **intravitreal steroids as the reference steroid strategy** in DME because they deliver reproducible anatomical drying and clinically meaningful, durable vision gains, at the known expense of cataract acceleration and IOP monitoring (Boyer et al., 2014; Pearson et al., 2011; Patil et al., 2023). **Topical steroids are a compelling, non-invasive prospect**, with OCS-01 showing early, randomized signals that justify optimism yet not replacement of intravitreal therapy; definitive year-long outcomes, safety characterization, and cost-effectiveness are essential before widespread adoption (Stefansson et al., 2023; Oculis, 2023). Clinicians should individualize therapy: consider intravitreal implants earlier in **pseudophakia** and **anti-VEGF non-response**, and reserve topical options for clinical trials or carefully monitored cases where injections are unacceptable or impractical, in alignment with current practice guidance (American Academy of Ophthalmology, 2025).

5.0 Conclusion

Diabetic macular edema (DME) remains a major cause of visual loss worldwide, and effective management requires balancing efficacy, safety, treatment burden, and patient preferences. This review synthesized evidence from randomized trials, meta-analyses, and real-world studies to compare **intravitreal corticosteroids** with **emerging topical steroid formulations**.

The findings consistently demonstrate that **intravitreal corticosteroids remain the benchmark within the steroid class**. High-quality evidence from large trials such as MEAD and FAME confirms that dexamethasone and fluocinolone acetonide implants achieve significant and durable improvements in best-corrected visual acuity (BCVA) and central retinal thickness (CST). These benefits, however, are accompanied by predictable safety trade-offs, particularly cataract progression and intraocular pressure (IOP) elevation, which require vigilant follow-up and, in some cases, surgical intervention. Despite these risks, intravitreal steroids are especially valuable in **pseudophakic eyes**, in **patients who respond poorly to anti-VEGF therapy**, and in those for whom frequent clinic visits are impractical.

By contrast, **topical steroids are still in an investigational phase**. Difluprednate drops have shown modest benefits in small studies but with notable IOP rise in a subset of patients. More promising results have emerged from **OCS-01**, a novel dexamethasone suspension with nanoparticle delivery, which has demonstrated meaningful short-term BCVA and CST improvements in Phase 2/3 and Phase 3 Stage 1 trials. Nevertheless, the absence of long-term data, the need for multi-daily dosing, and the lack of direct comparisons with intravitreal therapy mean that topical options cannot yet be considered standard of care.

For clinicians, the practical implication is clear: **intravitreal steroids should remain the preferred steroid option** in carefully selected patients, while topical therapy may be considered only in research settings or highly selected cases where intravitreal treatment is not feasible.

Moving forward, the field requires **large, long-term randomized controlled trials directly comparing topical and intravitreal steroids** with standardized outcomes, extended follow-up, and cost-effectiveness analyses. Such evidence will determine whether topical formulations can shift from experimental promise to practical reality, potentially reshaping future treatment algorithms for DME.

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