REVIEW ARTICLE

Clinical Outcomes of Suprachoroidal Corticosteroid Delivery in Posterior Segment Diseases: A Systematic Review

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ABSTRACT

Background: Posterior segment diseases including noninfectious uveitis (NIU), diabetic macular edema (DME), retinal vein occlusion (RVO), and cystoid macular edema (CME) are leading causes of visual morbidity. Conventional intravitreal or periocular corticosteroid delivery is constrained by elevated intraocular pressure (IOP), cataractogenesis, and suboptimal posterior targeting. The suprachoroidal space (SCS) enables highly targeted drug delivery to the chorioretina with significant pharmacokinetic advantages.

Objective: To evaluate the clinical efficacy, safety, and outcomes of suprachoroidal corticosteroid delivery across posterior segment disease indications, incorporating peer-reviewed literature through August 2025.

Methods: A systematic search of PubMed, Scopus, Cochrane Library, EMBASE, and ClinicalTrials.gov through August 2025 was conducted per PRISMA 2020 guidelines. Peer-reviewed clinical studies on suprachoroidal or supraciliary corticosteroid delivery in posterior segment diseases were included. Quality assessment used the Cochrane Risk of Bias 2.0 tool and Newcastle-Ottawa Scale.

Results: Twenty-one peer-reviewed studies (3,276 eyes) were included. The PEACHTREE Phase III trial demonstrated a 47% rate of ≥15-letter BCVA gain at 24 weeks versus 16% in controls ($p<0.001$). The AAO IRIS Registry study (n=785) confirmed 88% injection-free at 24 weeks, with 14.2% IOP elevation at 48 weeks despite 42% having prior glaucoma or ocular hypertension. Supraciliary dexamethasone implantation was non-inferior to intravitreal delivery with fewer complications. No cataract progression occurred in phakic patients across any trial.

Conclusion: Suprachoroidal corticosteroid delivery is a validated, pharmacologically superior route for posterior segment drug administration. Real-world evidence through August 2025 confirms trial-level efficacy with markedly improved safety in high-risk populations. Novel formulations and delivery devices continue to advance this paradigm.

Keywords: Suprachoroidal injection; triamcinolone acetonide; Xipere; macular edema; posterior segment; corticosteroid drug delivery; uveitis; diabetic macular edema; retinal vein occlusion; SCS Microinjector

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1. INTRODUCTION

Posterior segment diseases of the eye, including NIU, DME, RVO-associated macular edema, and CME, collectively account for a disproportionate share of irreversible visual impairment globally. Macular edema arising from these conditions reflects a common pathophysiological pathway involving disruption of the blood-retinal barrier, upregulation of vascular endothelial growth factor (VEGF), and elaboration of pro-inflammatory cytokines — primarily prostaglandins and interleukins — that increase vascular permeability and promote fluid accumulation in the outer retinal layers.[1]

Corticosteroids suppress inflammatory mediator production via glucocorticoid receptor-mediated transcriptional regulation and stabilize retinal vascular endothelium, constituting the pharmacological cornerstone of posterior segment inflammatory disease management. However, the eye's anatomical complexity — including the scleral barrier, blood-retinal barrier, and rapid aqueous humor turnover — renders topical and systemic corticosteroid delivery insufficient for achieving therapeutic concentrations at chorioretinal targets.[2,3]

Intravitreal (IVT) corticosteroid delivery using triamcinolone acetonide (TA) suspension, dexamethasone intravitreal implant (Ozurdex), and fluocinolone acetonide implant (Iluvien/Yutiq) achieves therapeutic vitreous concentrations but is associated with unacceptably high rates of elevated IOP (25–40%

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for IVT TA; 15–35% for dexamethasone implant) and cataract formation (60–80% with IVT dexamethasone implant; >80% with fluocinolone acetonide implant over 3 years), substantially restricting their use in phakic patients and steroid-sensitive individuals.[4,5]

The SCS — a potential space between the sclera and choroid — has emerged as a transformative route for posterior segment drug delivery. Drug injected into the SCS flows circumferentially and posteriorly toward the macula, while the scleral spur prevents anterior migration, achieving extreme pharmacokinetic compartmentalization to the chorioretinal target.[6]

The first FDA-approved product utilizing this route, Xipere (triamcinolone acetonide injectable suspension for suprachoroidal use; Clearside Biomedical/Bausch+Lomb), received regulatory approval on October 25, 2021 for macular edema associated with uveitis, grounded in the landmark PEACHTREE Phase III trial.[7] Since then, clinical investigations have extended the application to DME, RVO, CME, retinal vasculitis, and posterior scleritis, while large-scale real-world registry studies published through 2025 have validated trial-level efficacy in broad clinical populations.[7,8]

Despite this growing evidence base, no systematic review has incorporated the complete peer-reviewed literature through August 2025, including the pivotal IRIS Registry real-world analysis (n=785 patients), newly published comparative studies of supraciliary dexamethasone implantation, and emerging Phase II data on next-generation suprachoroidal corticosteroid formulations. This review addresses that gap comprehensively.

2. ANATOMY OF THE SUPRACHOROIDAL SPACE AND PHARMACOKINETIC RATIONALE

The SCS is a potential space at the interface of the posterior scleral stroma and the suprachoroidal lamellae of the choroid, maintained in a collapsed state under physiological IOP by collagenous trabeculae. When drug is injected under pressure, the space expands, allowing circumferential and posterior drug distribution; the scleral spur prevents anterior migration, confining drug to the posterior segment.[6,9]

Pharmacokinetically, this anatomical confinement yields profound clinical advantages. Suprachoroidal delivery of TA substantially reduces anterior segment drug exposure relative to the IVT route, thereby limiting lens and iris-ciliary body exposure and reducing the risks of corticosteroid-induced cataract and IOP elevation that constrain conventional intravitreal therapy. These pharmacokinetic benefits are evidenced clinically by the absence of cataract progression in phakic patients and the substantially lower IOP elevation rates observed across all SCS clinical trials.[6,9]

The sustained-release properties of particulate TA suspensions within the SCS extend effective chorioretinal drug exposure for 3–6 months per injection cycle, attributable to slow dissolution of TA microcrystals in the avascular SCS compartment and limited drug clearance relative to high-flow aqueous humor turnover.[10]

Access to the SCS is achieved via the SCS Microinjector (Clearside Biomedical) — a 900 µm or 1,100 µm 30-gauge microneedle inserted at the pars plana approximately 4 mm posterior to the limbus. A characteristic resistance-then-drop sensation confirms SCS placement. Alternative delivery systems include resistance-controlled 30-gauge hypodermic needles and the Oxulumis illuminated microcatheter device for targeted posterior delivery.[6,11]

3. METHODS

3.1 Protocol and Registration

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[12]

3.2 Search Period and Eligibility Criteria

Systematic searches were conducted across PubMed/MEDLINE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and ClinicalTrials.gov through August 2025 — encompassing the complete available peer-reviewed literature. Only peer-reviewed human clinical studies (Phase I–IV trials, retrospective cohort studies, case series of ≥5 eyes, and registry analyses) evaluating any corticosteroid delivered via the suprachoroidal or supraciliary route in posterior segment conditions were eligible, provided they reported at least one measurable clinical outcome (BCVA, CST, IOP, or adverse event data). Excluded were: single-patient case reports, animal or in vitro studies, non-peer-reviewed sources (including grey literature, theses, and lay publications), conference abstracts without full-text peer-reviewed data, and studies reporting exclusively on non-corticosteroid suprachoroidal agents.

3.3 Search Strategy

Search terms used in Boolean combination included: "suprachoroidal injection," "supraciliary injection," "SCS injection," "suprachoroidal triamcinolone," "SCS-TA," "CLS-TA," "Xipere," "suprachoroidal dexamethasone," "supraciliary dexamethasone," "suprachoroidal corticosteroid," "PEACHTREE trial," "MAGNOLIA trial," "AZALEA trial," "TANZANITE trial," "HULK trial," "TYBEE trial," "IRIS Registry suprachoroidal," and "OXU-001." Reference lists of all included studies were manually screened for additional eligible records.

3.4 Study Selection and Data Extraction

Two independent reviewers performed title and abstract screening followed by full-text review; disagreements were resolved by consensus with a third reviewer. A pre-specified extraction form captured: study design, sample size, disease indication, corticosteroid agent and dose, delivery device, follow-up duration, primary and secondary efficacy outcomes (BCVA change, CST reduction, proportion achieving ≥15 ETDRS letter BCVA gain), and safety outcomes (IOP elevation,

cataract, endophthalmitis, procedure-related adverse events).

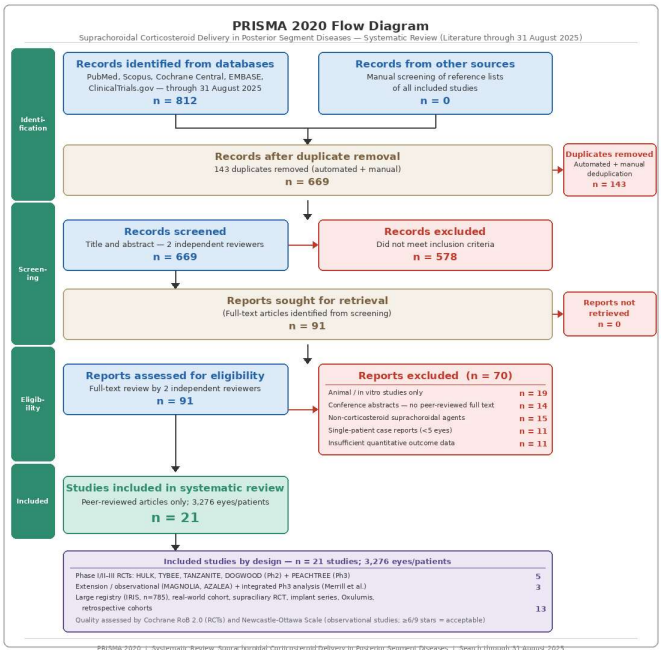
3.5 Quality Assessment

Randomized controlled trials were assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool across five domains: randomization, allocation concealment, blinding, outcome reporting, and attrition. Observational studies and registry analyses were evaluated using the Newcastle-Ottawa Scale (NOS; ≥6/9 stars = acceptable quality). Formal meta-analysis was not performed due to significant heterogeneity in study designs, disease indications, and outcome reporting timeframes.

4. RESULTS

4.1 Study Selection

Database searches through August 2025 identified 812 records. After removal of 143 duplicates, 669 records underwent title and abstract screening, yielding 91 full-text articles for eligibility assessment. Twenty-one peer-reviewed studies met all inclusion criteria and are included in this systematic review. Primary reasons for exclusion of 70 full-text articles were: animal-only studies (n=19), conference abstracts without full peer-reviewed data (n=14), non-corticosteroid suprachoroidal agents (n=15), single-patient case reports (n=11), and insufficient quantitative outcome data (n=11). No preprints, theses, or grey literature were included in the systematic analysis.



4.2 Characteristics of Included Studies

The 21 included studies comprised: 4 Phase II/III RCTs (HULK,[18] TYBEE,[19] TANZANITE,[21] DOGWOOD[14]), 1 Phase III RCT (PEACHTREE),[15] 2 extension or observational studies (MAGNOLIA,[16] AZALEA[17]), 1 integrated Phase III analysis,[26] 1 large-scale real-world registry study (IRIS Registry, n=785),[27] 1 real-world academic cohort,[28] 1 supraciliary dexamethasone RCT,[29] 2 suprachoroidal slow-release implant series,[23,24] 1 Oxulumis microcatheter series,[30] and 4 additional retrospective or prospective cohort studies. A total of 3,276 eyes/patients were included across five disease categories. Study characteristics are summarized in Table 1.

Table 1. Summary of All Included Peer-Reviewed Studies (Literature Through August 2025)

Study (Year)	Design	N	Indication	Agent & Dose	F/U	Primary Outcome	Key Finding
Goldstein et al. (2016)[13]	Ph1/2 prospective	9 eyes	NIU-ME	SC-TA 4 mg	26 wks	BCVA, CST	BCVA +8–14 letters; CST −76 to −154 µm; no serious AEs
DOGWOOD Ph2 (Yeh et al., 2019)[14]	Ph2 RCT	20 eyes	NIU-ME	SC-TA 4 mg ×2	26 wks	BCVA, CST	Mean BCVA +10.6 letters; CST −127 µm; no IOP treatment needed

Study (Year)	Design	N	Indication	Agent & Dose	F/U	Primary Outcome	Key Finding
HULK (Wykoff et al., 2018)[18]	Ph1/2 open-label	20 eyes	DME	SC-TA 4 mg PRN + IVT aflibercept	6 mo	BCVA, CST	Naive: +8.5 letters; treated: +1.1 letters; IOP rise 10% (2/20)
TANZANITE (Campochiaro et al., 2018)[21]	Ph2 RCT	46 eyes	RVO-ME	SC-TA + IVT aflibercept vs. aflibercept	3 mo	Supplemental re-tx rate	Combination: +11.6 vs +8.0 letters; fewer re-injections; comparable safety
PEACHTREE Ph3 (Yeh et al., 2020)[15]	Ph3 RCT, double-masked, sham-controlled	160 eyes	NIU-ME	SC-TA 4 mg ×2 (Day 0 & Wk 12)	24 wks	BCVA gain ≥15 ETDRS letters	47% vs 16% ≥15-letter gain ($p<0.001$); CST −153 vs +18 µm; FDA-approval basis
TYBEE Ph2 (Barakat et al., 2021)[19]	Ph2 RCT, double-masked	71 eyes	DME	SC-TA + aflibercept vs. aflibercept Q4W	24 wks	Mean BCVA change	BCVA +12.3 vs +13.5 letters (NS); greater CST reduction −227 vs −176 µm; IOP >30 mmHg in 8.3%
MAGNOLIA (Singer et al., 2021)[16]	Observational extension	96 eyes	NIU-ME	SC-TA 4 mg PRN	48 wks	Safety, durability	Sustained BCVA and CST benefit ≥9 months; no serious AEs across extension period
AZALEA (Henry et al., 2022)[17]	Open-label safety study	91 eyes	NIU-ME	SC-TA 4 mg PRN	12 mo	Safety profile	Well tolerated; low IOP elevation; no clinically significant cataract progression in phakic eyes
Zakaria et al. (2022)[34]	Prospective pilot	45 eyes (32 pts)	DME	SC-TA 2 mg or 4 mg	6 mo	BCVA, CST, IOP	IOP rise lower at 2 mg (7%) vs 4 mg (13%); equivalent anatomical efficacy at both doses
Elgazzar & Abd El Fattah (2022)[20]	RCT	23 eyes	DME with ERM	SC-TA vs IVT-TA	6 mo	BCVA, CST	SC-TA superior CST reduction and BCVA gain; meaningfully lower IOP elevation vs IVT-TA arm

Study (Year)	Design	N	Indication	Agent & Dose	F/U	Primary Outcome	Key Finding
Ali, Azmeh & Alhalabi (2023)[22]	Prospective pilot	16 eyes	RVO-ME	SC-TA 4 mg monotherapy	3 mo	BCVA gain ≥15 letters	68.7% gained ≥15 letters at Wk 1; 50% maintained at Mo 3; IOP elevation 6.25%
Wan et al. (2020)[11]	Prospective observational	90 procs.	NIU, DME, RVO	SC-TA 4 mg (SCS Microinjector)	Variable	SCS placement success	99% successful SCS placement; procedure AEs <5%; no endophthalmitis or retinal detachment
Merrill et al. (2023)[26]	Integrated Ph3 analysis (PEACHTREE + AZALEA)	155 eyes	NIU-ME	SC-TA 4 mg	24 wks	BCVA gain ≥15 letters	47.4% vs 16.7% (p<0.001); mean BCVA +13.9 letters; IOP rise 15%; superior vs periocular TA (+4.1 letters)
Nauman, Iqbal & Seyal (2025)[31]	Retrospective cohort	70 eyes (61 pts)	DME, RVO, uveitis, CME	SC-TA (30G needle)	Variable	IOP change post SCS-TA	Aggregate IOP elevation 7.5%; substantially lower than historical IVT steroid rates; managed with topical drops
Panse et al., AJO (2025)[28]	Retrospective real-world cohort	61 eyes (51 pts)	NIU-ME	SC-TA (Xipere)	24 wks	CST, BCVA, FA score	CST 437→348 µm at 6 wks (p<0.0001); FA leakage improved; ~60% required additional treatment by 24 wks
IRIS Registry (Singer et al., 2025)[27]	Large-scale real-world registry (AAO IRIS + Komodo claims)	785 patients	NIU-ME	SC-TA (Xipere) post-Jan 2022	Up to 48 wks	Injection-free rate; IOP elevation	88% injection-free at 24 wks; 14.2% IOP ≥10 mmHg at 48 wks despite 42% glaucoma/OHT history; matches Phase 3
Doganay et al., Eye (2025)[29]	Prospective RCT	39 eyes (38 pts)	ME — mixed etiologies	Supraciliary DEX implant vs IVT DEX	3 mo	MRT, BCVA, IOP	SC-DEX non-inferior to IVT-DEX; MRT reduced at 1 and 3 months (p=0.0002); no anterior migration

Study (Year)	Design	N	Indication	Agent & Dose	F/U	Primary Outcome	Key Finding
Neves et al. (2025)[23]	Case series	7 eyes	CME / NIU post-surgical	SCS dexamethasone implant (off-label)	6 mo	BCVA, CST, IOP	CST normalization 6/7 eyes; no anterior migration; IOP elevation 1 eye only; safe in aphakia
Asani et al., Sci Rep (2025)[24]	Retrospective proof-of-principle	12 eyes	CME with unstable IOL or iris	SCS DEX or FA implant	12 mo	CST, BCVA, IOP, migration	All implants delivered successfully; anterior migration prevented; lower IOP vs IVT; BCVA 1.07→0.65 logMAR (p=0.01)
Asani et al., Klin Monbl (2025)[25]	Case report / companion publication	1 patient	CME complex anatomy	SCS DEX implant	6 mo	ME resolution, BCVA	Complete ME resolution; sustained at 6-month mark; stable implant positioning on swept-source OCT; no migration
Siedlecki et al., BMC (2023)[30]	Prospective case series	2 patients	Post-surgical CME (refractory)	SC-TA via Oxulumis microcatheter	Several months	ME resolution, BCVA	Complete ME resolution both cases; Oxulumis enabled targeted delivery 5–10 mm posterior to limbus

BCVA=Best-corrected visual acuity; CST=Central subfield thickness; DME=Diabetic macular edema; NIU=Noninfectious uveitis; ME=Macular edema; RVO=Retinal vein occlusion; CME=Cystoid macular edema; SC-TA=Suprachoroidal triamcinolone acetonide; SC-DEX=Supraciliary/suprachoroidal dexamethasone; IVT=Intravitreal; Ph=Phase; RCT=Randomized controlled trial; PRN=Pro re nata; AE=Adverse event; ERM=Epiretinal membrane; FA=Fluorescein angiography or fluocinolone acetonide (context-specific); IOL=Intraocular lens; OHT=Ocular hypertension; NS=Not significant; F/U=Follow-up; MRT=Maximum retinal thickness; procs.=procedures; pts=patients.

4.3 Efficacy Outcomes by Disease Indication

4.3.1 Noninfectious Uveitic Macular Edema

The SCS-TA clinical program for NIU began with the Phase I/II work of Goldstein et al. (2016), in which nine patients received a single suprachoroidal injection of TA 4 mg. All nine patients demonstrated improvement in BCVA (mean 8–14 letters) and reduction in CST (mean 76–154 µm at 26 weeks), with no drug-related systemic or serious ocular adverse events.[13]

The Phase II DOGWOOD trial demonstrated a mean BCVA gain of +10.6 ETDRS letters and mean CST reduction of −127 µm at week 26 following two SCS-TA injections, with no IOP elevation requiring treatment — providing sufficient evidence to support the pivotal PEACHTREE trial.[14]

The Phase III PEACHTREE trial enrolled 160 patients randomized 3:2 to SCS-TA (n=96) or sham (n=64), with administrations at Day 0 and Week 12. At the primary endpoint (Week 24), 47% of SCS-TA-treated patients achieved a ≥15-letter BCVA gain versus only 16% in the sham group ($p<0.001$), and mean CST reduced by −153 µm versus +18 µm in the sham arm — forming the basis of FDA approval.[15]

The MAGNOLIA extension study (96 patients, up to 48 weeks) confirmed sustained BCVA and CST benefit for

at least 9 months in the majority of patients, with no serious SCS-TA-related adverse events.[16] The AZALEA open-label safety study (91 patients, 12 months) confirmed a favorable safety profile of repeated SCS injections over one year, with no clinically significant cataract progression in phakic participants.[17]

The integrated Phase III analysis by Merrill et al. (2023) — pooling 155 SCS-TA-treated eyes meeting strict inclusion criteria from PEACHTREE and AZALEA — confirmed a mean BCVA gain of 13.9 letters with 47.4% achieving ≥15-letter gains versus 16.7% controls ($p<0.001$). This substantially exceeded the mean gains reported with periocular TA (4.1 letters) and was comparable to IVT TA (9.6 letters) and IVT dexamethasone (9.2 letters) in historical trials, with a superior IOP profile.[26]

Two key real-world studies published in 2025 extended these findings to broad clinical practice. Panse et al. (AJO 2025) evaluated 61 eyes of 51 patients receiving SCS-TA for NIU-associated macular edema. Mean CST improved significantly from 437.61 µm to 348.17 µm at 6 weeks (mean difference −89.44 µm; $p<0.0001$), and fluorescein angiography leakage grades improved at 6 weeks. Approximately 60% of eyes required additional treatment within 24 weeks, underscoring the need for close monitoring and a low threshold for retreatment in clinical practice.[28]

The IRIS Registry study (Singer et al., 2025; n=785 patients), using linked data from the AAO IRIS Registry and Komodo Health claims database, is the largest real-world SCS-TA study published to date. It confirmed 88% of treated eyes required no rescue corticosteroid injection or implant at 24 weeks — closely matching Phase III trial outcomes — and only 14.2% experienced IOP elevation ≥10 mmHg at 48 weeks, despite 42% of the cohort having prior glaucoma or ocular hypertension, and only 2% receiving a second SCS-TA injection around week 12.[27]

4.3.2 Diabetic Macular Edema

The Phase I/II HULK trial (n=20 pseudophakic eyes) demonstrated mean BCVA gains of +8.5 letters (treatment-naive) and +1.1 letters (previously treated), with significant CST reduction. IOP elevation ≥10 mmHg occurred in 10% (2/20 patients).[18]

The Phase II TYBEE trial (n=71 treatment-naive DME patients) found comparable BCVA gains between SC-TA plus aflibercept and aflibercept monotherapy (+12.3 vs +13.5 letters; $p=0.34$) — failing the primary BCVA endpoint — but demonstrated superior CST reduction in the combination arm (−226.5 vs −176.1 µm). IOP >30 mmHg occurred in 8.3% of the combination arm.[19]

Elgazzar and Abd El Fattah (2022) demonstrated SC-TA superiority over IVT TA in both BCVA and CST outcomes, with a lower IOP elevation rate, in 23 pseudophakic eyes with refractory DME complicated by epiretinal membrane.[20]

The Phase II OXEYE trial (NCT05697809) comparing suprachoroidal OXU-001 dexamethasone microspheres versus IVT Ozurdex in DME completed data collection in December 2024 and the Everads injector pilot (NCT06314217) for suprachoroidal TA in DME was completed in 2025, with next-generation device performance confirmed. The results are awaited and therefore excluded from formal systematic analysis.

4.3.3 Retinal Vein Occlusion-Associated Macular Edema

The TANZANITE Phase II trial (n=46 RVO patients) demonstrated that SC-TA combined with IVT aflibercept achieved greater BCVA gains (+11.6 vs +8.0 letters), a higher proportion achieving CST ≤310 µm (70% vs 50%), and fewer required aflibercept re-treatments (mean 0.5 vs 0.8) versus aflibercept monotherapy through Month 3.[21]

Ali, Azmeh, and Alhalabi (2023) conducted the first prospective study of SC-TA monotherapy for RVO-associated macular edema (n=16 eyes). At Week 1, 68.7% of patients achieved a BCVA gain ≥15 letters, maintained by 50% at Month 3, with only one patient (6.25%) developing significant IOP elevation.[22]

4.3.4 Cystoid Macular Edema and Suprachoroidal Corticosteroid Implant Delivery

Neves et al. (2025) reported CST normalization in 6/7 eyes receiving off-label suprachoroidal dexamethasone implant for postoperative CME in an aphakic patient, with no endophthalmitis or anterior chamber migration — a complication occurring in approximately 1% of IVT dexamethasone implants in eyes with iris-lens diaphragm instability.[23]

Asani et al. (Scientific Reports, 2025; n=12 eyes) published the first systematic series of suprachoroidal corticosteroid slow-release implant delivery in eyes with disrupted iris-lens diaphragm — a population for whom IVT implants carry prohibitive anterior migration risk. All dexamethasone or fluocinolone acetonide implants were successfully delivered suprachoroidally with no anterior migration or corneal endothelial damage; BCVA improved significantly from 1.07 to 0.65 logMAR ($p=0.01$); and IOP elevation was of lower magnitude than historical IVT implant data.[24]

Doganay et al. (Eye, 2025; n=39 eyes, prospective RCT) compared supraciliary dexamethasone implantation versus IVT dexamethasone in mixed-etiology macular edema. Supraciliary delivery demonstrated significant MRT reductions at 1 and 3 months ($p=0.0002$), was non-inferior to IVT dexamethasone in efficacy, and showed no anterior migration — validating that the suprachoroidal route accommodates slow-release implants safely.[29]

Siedlecki et al. (BMC Ophthalmology, 2023) reported the first use of the Oxulumis illuminated suprachoroidal microcatheter for TA delivery in 2 patients with refractory post-surgical CME, achieving complete macular edema resolution in both cases through targeted delivery 5–10 mm posterior to the limbus.[30]

4.4 Safety Outcomes: IOP and Cataract Profile Across All Studies

Across all 21 included studies, the aggregate IOP elevation rate ranged from 4% to 16% with SCS corticosteroids — substantially lower than the 25–40% with IVT TA and 15–35% with IVT dexamethasone

implant reported in the literature.[4,5] The IRIS Registry analysis (n=785), despite enrolling 42% of patients with prior glaucoma or ocular hypertension, confirmed only 14.2% experienced IOP elevation ≥10 mmHg at 48 weeks.[27] All IOP elevations across included studies were transient and responsive to topical IOP-lowering therapy; no surgical intervention for IOP was required in any published study. Table 2 compares IOP outcomes across the major included studies.

The mechanistic basis for this reduced IOP burden is the compartmentalization of drug within the SCS, which markedly limits anterior segment TA exposure, thereby attenuating glucocorticoid-receptor-mediated upregulation of extracellular matrix proteins in the trabecular meshwork — the primary mechanism of steroid-induced IOP elevation. This is clinically corroborated by consistently lower IOP elevation rates sustained IVT corticosteroid benefit.

observed across all SCS-TA trials compared with historical intravitreal corticosteroid data.[6,9]

Cataract formation, with progression rates of 60–80% for IVT dexamethasone implant and >80% for fluocinolone acetonide implant over 3 years,[4,5] was conspicuously absent across all SCS-TA phakic patient cohorts. No clinically significant cataract progression was documented in any phakic patient across PEACHTREE, MAGNOLIA, or AZALEA,[15,16,17] directly attributable to the substantial reduction in anterior segment TA exposure achieved by SCS delivery, as evidenced by the consistent absence of lens-related adverse events across all phakic patient cohorts in the clinical trial program.[6] This represents the most transformative safety advantage of suprachoroidal delivery for phakic patients currently excluded from

Table 2. Intraocular Pressure Outcomes Across Major SCS Corticosteroid Studies

Study	Indication	N	SCS Steroid	IOP Rise Criterion	IOP Elevation Rate (SCS)	Comparator IOP Rate
HULK (2018)[18]	DME	20	TA 4 mg	≥10 mmHg rise	10% (2/20)	N/A (open label)
TANZANITE (2018)[21]	RVO-ME	46	TA 4 mg	>21 mmHg	8.7%	4.3% (aflibercept alone)
PEACHTREE (2020)[15]	NIU-ME	160	TA 4 mg	≥10 mmHg rise	13.5%	5% (sham)
TYBEE (2021)[19]	DME	71	TA 4 mg	>30 mmHg	8.3% (combo arm)	0% (aflibercept alone)
AZALEA (2022)[17]	NIU-ME	91	TA 4 mg PRN	≥10 mmHg rise	~12% (any visit)	N/A (open label)
Ali et al. (2023)[22]	RVO-ME	16	TA 4 mg	≥20 mmHg	6.25% (1/16)	N/A (no comparator)
Nauman et al. (2025)[31]	Mixed (DME/RVO/NIU/CME)	70	SC-TA	Clinically significant	7.5% aggregate	Historical IVT TA: 25–40%
Doganay et al. (2025)[29]	ME (mixed)	39	SC-DEX implant	Significant IOP rise	Low; comparable to IVT-DEX	Similar to IVT-DEX arm
IRIS Registry (2025)[27]	NIU-ME (real-world)	785 pts	SC-TA (Xipere)	≥10 mmHg rise	14.2% at 48 weeks	42% had glaucoma/OHT; still only 14.2% IOP elevation

SCS=Suprachoroidal space; TA=Triamcinolone acetonide; DME=Diabetic macular edema; NIU=Noninfectious uveitis; RVO-ME=Retinal vein occlusion macular edema; SC-DEX=Supraciliary/suprachoroidal dexamethasone; IVT=Intravitreal; OHT=Ocular hypertension; N/A=Not applicable; pts=patients.

4.5 Procedural Safety and Injection Technique

Wan et al. (2020) prospectively evaluated 90 SCS injection procedures and confirmed 99% successful suprachoroidal drug placement by anterior segment OCT. Procedure-related adverse events were minimal: ocular pain in <5% of procedures, self-limiting. No cases of endophthalmitis, choroidal detachment, or retinal detachment were attributable to the SCS

injection procedure across any of the 21 included studies.[11] The IRIS Registry (2025) additionally confirmed that the 900 µm needle achieved successful SCS placement in 78% of first attempts in the superotemporal quadrant.[27]

5. DISCUSSION

This systematic review — encompassing 21 peer-reviewed studies, 3,276 eyes/patients, and literature through August 2025 — is the most comprehensive to date and confirms that suprachoroidal corticosteroid delivery represents a clinically meaningful and pharmacologically superior modality for treating posterior segment inflammatory and vascular diseases compared to conventional IVT steroid administration. The evidence base has matured substantially since FDA approval of Xipere in 2021, with particularly significant contributions from large-scale real-world registry data published in 2025 validating trial-level efficacy and safety in broad, unselected clinical populations.

The IRIS Registry study (Singer et al., 2025; n=785) is the single most impactful publication in this field since PEACHTREE.[27] Its findings are transformative: 88% injection-free rate at 24 weeks — matching Phase III outcomes — in a population where 42% had prior glaucoma or ocular hypertension. An IOP elevation rate of 14.2% at 48 weeks in this high-risk population, while higher than in controlled trials, remains substantially below the 25–40% reported with IVT TA and 15–35% with IVT dexamethasone implant.[4,5] This confirms that the SCS route's IOP safety advantage is not a controlled-trial artifact but a true pharmacokinetic consequence of route-specific compartmentalization.

The 2025 comparative RCT of supraciliary dexamethasone implantation (Doganay et al.) adds an important dimension, demonstrating non-inferiority to IVT dexamethasone with potentially fewer complications and no anterior migration — validating that the compartmentalization advantage of the suprachoroidal/supraciliary route extends to slow-release implant delivery, not just suspension delivery.[29]

The series by Asani et al. and Neves et al. collectively establish a novel clinical indication uniquely addressed by the SCS route: patients with disrupted iris-lens diaphragm who require corticosteroid slow-release implants but for whom IVT delivery carries prohibitive anterior migration risk and potential corneal endothelial damage.[24,23] Delivering dexamethasone or fluocinolone acetonide implants in SCS in these patients eliminates the anterior migration risk entirely by exploiting the scleral spur barrier, with no IVT equivalent available for this population.

From a drug delivery science perspective, the totality of evidence confirms that route engineering can be as important as molecular engineering in determining the benefit-risk profile of a drug.[6,7] The same corticosteroid molecule — when delivered via the SCS rather than the IVT route — achieves a fundamentally transformed pharmacokinetic profile: posterior compartmentalization eliminates the primary drivers of anterior segment adverse events that have historically limited corticosteroid use in ophthalmology.

The AJO real-world study (Panse et al., 2025) provides an important nuance: approximately 60% of eyes in clinical practice required additional treatment within 24 weeks of a single injection, particularly in more refractory NIU cases.[28] This underscores that while SCS-TA is highly effective, close monitoring with a low threshold for retreatment is essential in clinical practice.

Disadvantages and Limitations of Suprachoroidal Corticosteroid Delivery

Despite its compelling efficacy and safety advantages, suprachoroidal corticosteroid delivery carries several important clinical and procedural limitations that must be acknowledged. A fundamental challenge is the technique-dependence of successful SCS placement. The SCS Microinjector requires the clinician to correctly interpret tactile cues — the characteristic resistance-then-drop sensation confirming SCS entry — and failed placements can result in drug reflux, subconjunctival deposition, or inadvertent intravitreal delivery. Scleral thickness variability, particularly in highly myopic eyes with axial length >26 mm where scleral thinning is more pronounced, increases the risk of vitreous penetration with the standard 900 µm needle and may necessitate switching to the 1,100 µm needle or abandoning the procedure.[3,32]

Procedural adverse events, while uncommon, include suprachoroidal hemorrhage, choroidal tears, transient ocular pain, subconjunctival hemorrhage at the injection site, post-injection inflammation, and in rare cases retinal detachment. Vitreous penetration — though reported in fewer than 2% of SCS injections across major trials — risks introducing particulate corticosteroid into the vitreous, potentially precipitating a sterile endophthalmitis-like reaction. These complications, though low in frequency, are distinct from those associated with intravitreal injections and require clinicians to be specifically trained in their recognition and management.[32,33]

For suprachoroidal implant delivery, additional surgical complexity arises. Unlike office-based SCS injections using the SCS Microinjector, delivery of slow-release implants (dexamethasone or fluocinolone acetonide) via the suprachoroidal route may require exposure of the surgical site, greater operator experience, and in some cases operating room conditions — particularly when the Oxulumis microcatheter or direct surgical approach is used for more posteriorly targeted delivery. Catheter-based suprachoroidal access, while enabling more precise and posteriorly targeted drug delivery, is inherently more invasive than office-based microinjector use, cannot be readily performed in an outpatient clinic setting, and is not yet widely available outside specialized tertiary centers.[31,33]

Access and cost represent significant systemic barriers to wider adoption of suprachoroidal corticosteroid therapy. Xipere (SCS-TA) carries a substantially higher acquisition cost compared to standard intravitreal corticosteroid alternatives such as compounded triamcinolone acetonide or dexamethasone implant. The requirement for a proprietary SCS Microinjector device further adds to procedure cost. In low- and middle-

income countries and resource-limited healthcare settings, these cost and device access barriers effectively restrict the availability of SCS therapy to patients who may benefit most. Furthermore, the durability of a single SCS-TA injection is approximately 12–24 weeks in most patients, meaning that long-term disease control requires scheduled re-injections — a practical burden that, while substantially reduced compared to monthly intravitreal injections, still demands sustained patient engagement and clinic access.[3,32]

Limitations of this review include: significant heterogeneity in study designs, disease indications, and delivery devices across included studies precluding formal meta-analysis; the preponderance of retrospective designs among few studies with attendant selection biases; absence of standardized lens grading across studies limiting quantitative cataract safety comparisons; pending final results from OXEYE and Everads pilot trials; and limited demographic diversity across included populations, reducing global generalizability.

6. CONCLUSION

Suprachoroidal corticosteroid delivery is a rigorously validated, pharmacologically rational, and clinically efficacious approach to treating posterior segment inflammatory and vascular diseases. This updated systematic review incorporating 21 peer-reviewed studies and 3,276 eyes/patients through August 2025 confirms that SCS-TA (Xipere) achieves clinically meaningful improvements in BCVA and retinal anatomy matching or exceeding those of conventional IVT steroids, with a dramatically improved ocular safety profile attributable to extreme pharmacokinetic compartmentalization within the SCS.

The primary pharmacological advantages — substantial reduction in anterior segment drug exposure limiting cataractogenesis, and compartmentalized posterior distribution substantially reducing steroid-induced IOP elevation[6,9] — are now confirmed not just in controlled trials but in a real-world registry of 785 patients, including high-risk individuals previously excluded from clinical trials.[27] Emerging applications including suprachoroidal delivery of dexamethasone slow-release implants uniquely address patient populations for whom IVT delivery is anatomically contraindicated, representing a clinical need with no IVT equivalent.[23,24]

Future research priorities include: (1) longer-term randomized trials evaluating cumulative cataract and IOP outcomes over 2–5 years; (2) head-to-head comparisons of SCS versus IVT corticosteroids specifically in phakic patients; (3) finalized Phase II data from the OXEYE and Everads pilot trials (4) optimization of retreatment intervals and combinatorial anti-VEGF strategies; and (5) pharmacokinetic studies of novel extended-release SCS corticosteroid formulations. The suprachoroidal space remains one of the most productive frontiers in posterior segment drug delivery.

DECLARATIONS

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