



EFFECTIVENESS OF THE INTRAVITREAL DEXAMETHASONE IMPLANT IN THE MANAGEMENT OF REFRACTORY UVEITIC MACULAR OEDEMA: A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS AND PRIMARY STUDIES

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ABSTRACT

Introduction. Macular oedema is the single most important structural cause of irreversible central visual loss in non-infectious uveitis, and a substantial proportion of eyes remain oedematous despite topical, periocular, systemic corticosteroid, immunomodulatory, or anti-VEGF therapy. The biodegradable 0.7 mg intravitreal dexamethasone implant (Ozurdex®) delivers sustained intravitreal corticosteroid over approximately six months and has become a widely used option for refractory disease, yet the magnitude, durability, and safety of its effect specifically in refractory uveitic macular oedema have never been quantified across the entire primary evidence base.

Methods. The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible: RCTs, prospective and retrospective cohorts, case-control, cross-sectional, and observational interventional

series with ≥ 5 eyes. Risk of bias assessed with RoB 2 and ROBINS-I; GRADE for certainty.

Results. Thirty-five reports from 33 independent study populations comprising 1,871 eyes. Central macular thickness fell by $-156.8 \mu\text{m}$ at month 1 (95%CI -184.9 to -128.7 ; $P < 0.0001$; $I^2 = 74.8\%$), $-146.2 \mu\text{m}$ at month 3, and $-101.1 \mu\text{m}$ at month 6. Best-corrected visual acuity improved by 0.160 logMAR at month 1 (95%CI -0.195 to -0.125 ; $P < 0.0001$; $I^2 = 0\%$), 0.186 logMAR at month 3, and 0.141 logMAR at month 6, equivalent to gains of 8, 9, and 7 ETDRS letters. Complete resolution of macular oedema was achieved in 79.0% (95%CI 65.9–89.8), a gain of ≥ 15 letters in 33.8% (95%CI 25.7–42.3), and vitreous haze score of 0 in 72.2% (95%CI 56.0–86.0). In the sham-controlled RCT, DEX-I quadrupled vitreous clearing (RR 3.95; 95%CI 2.04–7.62) and more than trebled 15-letter gain (RR 3.26; 95%CI 1.73–6.13). Median time to recurrence clustered between 6 and 9 months and 49.1% of eyes (95%CI 37.6–60.6) required re-implantation within six months. Clinically significant IOP elevation occurred in 20.7% (95%CI 14.4–27.7) and cataract progression in 23.0% of phakic eyes (95%CI 12.5–35.4); glaucoma surgery ($\approx 1.1\%$) and endophthalmitis (0.11%) were rare. Meta-regression showed greater baseline CMT predicted larger absolute reduction ($\beta = -0.71 \mu\text{m}$ per μm ; $R^2 = 68.2\%$; $P = 0.006$). An exploratory multivariable prognostic model achieved AUC 0.734.

Discussion. The pooled effect sizes confirm that a single dexamethasone implant reverses the great majority of retinal thickening in refractory uveitic macular oedema within one month, with maximal anatomical and functional benefit between months 1–3, and approximately one third lost by month 6—consistent with the six-month pharmacokinetic profile of PLGA matrix

degradation. Heterogeneity was substantial for anatomical but negligible for functional outcomes, indicating variability lies principally in baseline oedema severity.

Conclusion. In refractory uveitic macular oedema, the 0.7 mg intravitreal dexamethasone implant produces clinically substantial improvement in macular thickness, visual acuity, and intraocular inflammation with a predictable and manageable safety profile. Because approximately half of treated eyes recur within six months, DEX-I should be planned as a repeatable component of a structured long-term strategy, with pre-emptive re-treatment around month 4–5, mandatory IOP surveillance, and consideration of a longer-acting fluocinolone acetonide implant in eyes with repeated early recurrence.

Keywords: uveitis; macular oedema; dexamethasone intravitreal implant; Ozurdex; optical coherence tomography; central macular thickness; visual acuity; ocular hypertension; systematic review.

INTRODUCTION

Background

Uveitis encompasses a heterogeneous group of intraocular inflammatory disorders that together account for approximately 5–10 % of legal blindness worldwide and a disproportionate share of visual disability in working-age adults, because the disease characteristically affects individuals in their third to fifth decades and follows a chronic relapsing course. Within this spectrum, macular oedema is the single most frequent and most consequential structural complication, arising in roughly one third of eyes with intermediate, posterior or panuveitis and accounting for the majority of permanent central visual loss.^{1,2,73}

The pathophysiology of uveitic macular oedema is fundamentally distinct from that of the diabetic or vaso-occlusive varieties. The dominant event is a cytokine-driven breakdown of the inner and outer blood–retinal barriers. Tumour necrosis factor- α , interleukin-1 β , interleukin-6, interleukin-8, interleukin-17 and CCL2 released by activated T lymphocytes, retinal microglia, Müller glia and the retinal pigment epithelium downregulate the tight-junction proteins zonula occludens-1, occludin and claudin-5, disrupt the adherens junction complex, and increase transcellular caveolar transport. The resulting paracellular and transcellular leakage of plasma protein into the outer plexiform and inner nuclear layers raises interstitial oncotic pressure, and, when the transport capacity of the Müller cells and the retinal pigment epithelium is exceeded, intraretinal cystoid spaces and subretinal fluid accumulate. Vascular endothelial growth factor participates in this cascade but occupies a subordinate position relative to the pro-inflammatory cytokine network — which explains, in mechanistic terms, why anti-vascular endothelial growth factor monotherapy so frequently fails in inflammatory macular oedema.^{1,3,4,72}

Corticosteroids remain the therapeutic cornerstone precisely because they act upstream of the entire cascade: through the glucocorticoid receptor they suppress nuclear factor- κ B and activator protein-1 mediated transcription of the pro-inflammatory cytokine repertoire, restore tight-junction protein expression, inhibit phospholipase A2 and thereby prostaglandin synthesis, and reduce vascular endothelial growth factor production. Their route of delivery, however, dictates the therapeutic index. Systemic corticosteroids and immunomodulators expose the patient to hyperglycaemia, hypertension, osteoporosis, adrenal suppression, infection and cytopenias; topical and periocular preparations achieve inadequate

and short-lived posterior segment concentrations. Sustained intraocular delivery therefore represents a rational compromise.^{5,6,7}

The biodegradable 0.7 mg dexamethasone intravitreal implant is a rod-shaped poly(D,L-lactide-co-glycolide) device injected through a 22-gauge applicator in an office-based, sutureless procedure. The polymer matrix hydrolyses progressively to carbon dioxide and water, releasing dexamethasone in a biphasic manner with peak vitreous and retinal concentrations during the first two months and detectable, therapeutically relevant levels for up to six months. Experimental models of anterior and intermediate uveitis have confirmed that the implant achieves target-tissue concentrations sufficient to abolish cellular infiltration while limiting systemic exposure. Regulatory approval was granted for non-infectious posterior segment uveitis on the basis of the HURON randomised sham-controlled trial, and subsequent indications now include diabetic macular oedema and macular oedema secondary to retinal vein occlusion.^{7,8,9,10}

Refractory uveitic macular oedema as a distinct clinical problem

The term refractory, as applied in this review, denotes macular oedema that persists, recurs or progresses despite an adequate trial of at least one conventional modality — topical or periocular corticosteroid, systemic corticosteroid, a conventional or biologic immunomodulatory agent, or intravitreal anti-vascular endothelial growth factor therapy — or that recurs each time such therapy is withdrawn. Eyes meeting this definition differ systematically from treatment-naïve eyes: they have longer oedema duration, a higher prevalence of epiretinal membrane, disorganisation of the retinal inner layers and disruption of the external limiting membrane and ellipsoid zone, more frequent prior pars plana vitrectomy, and a higher probability of established photoreceptor loss. These structural differences attenuate both the anatomical and the functional ceiling of any subsequent intervention and are precisely the covariates evaluated in the prognostic analysis presented here.^{16,20,57,59}

Research gap

Three specific evidentiary deficiencies motivated this review. First, existing syntheses are either restricted to a single administration of the implant and to seven small cohorts, or address the broader category of non-infectious intermediate, posterior and panuveitis rather than the specific and clinically distinct problem of refractory macular oedema. Second, no previous synthesis has modelled the time course of the effect across months 1, 3 and 6 as separate pooled estimates, despite the fact that the pharmacokinetics of the implant make the

shape of that curve the principal determinant of re-treatment scheduling. Third, and most importantly, although several primary studies have identified baseline predictors of response — epiretinal membrane, oedema duration, outer retinal band integrity, lens status, age and prior vitrectomy — no synthesis has combined them into a single prognostic construct or quantified their discriminative performance.^{45,46,47,51}

Novelty of the present review

This review advances the field in five respects. It is the first synthesis restricted to refractory uveitic macular oedema that simultaneously incorporates randomised and observational primary evidence while explicitly excluding secondary literature from the characteristics table and from all quantitative pooling. It provides thirteen pre-specified outcome domains, substantially exceeding the two to four domains covered by earlier reviews. It models the anatomical and functional treatment effect as an explicit temporal trajectory with separate random-effects estimates at months 1, 3 and 6. It reconstructs recurrence-free survival curves from published medians and landmark estimates, allowing the durability of the implant to be visualised across five independent cohorts. Finally, it derives an exploratory multivariable prognostic model of anatomical response and evaluates its discrimination and calibration by receiver operating characteristic analysis, providing the first quantitative estimate of how well routinely available baseline variables can identify the eyes most likely to benefit.^{45,46,47}

Objectives

The general objective was to determine the effectiveness and safety of the 0.7 mg intravitreal dexamethasone implant in the treatment of refractory uveitic macular oedema. The specific objectives were:

- to quantify the pooled change in central macular thickness at months 1, 3 and 6;
- to quantify the pooled change in best-corrected visual acuity at months 1, 3 and 6;
- to estimate the pooled proportions of eyes achieving complete resolution of macular oedema, a gain of at least 15 ETDRS letters, and a vitreous haze score of zero;
- to characterise the durability of the therapeutic effect, the median time to recurrence, the re-implantation requirement and the mean number of implants;
- to determine the corticosteroid- and immunomodulator-sparing effect;
- to quantify the incidence of intraocular pressure elevation, cataract progression and serious ocular adverse events;
- to derive and evaluate an exploratory prognostic model for anatomical response; and

- to appraise the certainty of the evidence for each outcome domain using GRADE.

Hypotheses

Null hypothesis (H^0). The 0.7 mg intravitreal dexamethasone implant produces no statistically significant change in central macular thickness or best-corrected visual acuity from baseline in eyes with refractory uveitic macular oedema, and no meaningful difference relative to comparator intravitreal therapies.

Alternative hypothesis (H^1). The 0.7 mg intravitreal dexamethasone implant produces a statistically significant and clinically meaningful reduction in central macular thickness and improvement in best-corrected visual acuity, maximal between months 1 and 3 and attenuating by month 6, superior to intravitreal methotrexate and ranibizumab and non-inferior to intravitreal triamcinolone acetonide, at the cost of a predictable and largely medically manageable increase in intraocular pressure and in the rate of cataract progression.

Anticipated benefits of the review

For the practising ophthalmologist and uveitis specialist, the review supplies numerical effect estimates and a defined temporal profile that permit re-treatment to be scheduled pre-emptively rather than reactively, together with quantified risk figures that support genuinely informed consent. For the health-system planner, the pooled re-implantation rate and mean number of implants provide the parameters needed to model resource use and to compare the implant with longer-acting devices and with systemic biologic therapy. For the researcher, the identification of imprecise domains, the demonstration of small-study effects and the exploratory prognostic model define a concrete agenda for the adequately powered randomised trials and individual-participant-data analyses that the field still lacks.^{48,49,50}

METHODS

Protocol, registration and reporting standard

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, and the 27-item PRISMA checklist was completed in full. The review protocol was written a priori and specified the population, intervention, comparators, the thirteen outcome domains, the eligibility criteria, the risk-of-bias instruments and the statistical approach before any data were extracted. Deviations from the protocol were limited to the post-hoc addition of the reconstructed recurrence-free survival analysis and of the exploratory prognostic model, both of which are explicitly labelled as exploratory throughout. Because

the review used only aggregate data from previously published reports, institutional ethical approval and individual patient consent were not required.⁶⁷

Eligibility criteria

Eligibility was framed using the PICOS structure detailed in Table 1. In accordance with the pre-specified design restriction, only randomised controlled trials, cohort studies, case-control studies, cross-sectional studies and other observational, prospective or retrospective interventional designs with at least five eyes were eligible for the characteristics table and for quantitative synthesis. Systematic reviews and meta-analyses identified during screening were deliberately excluded from the characteristics table and from all pooled estimates, but were retained and are discussed in Section 4 as contextual comparators, in keeping with the pre-specified handling of secondary literature.⁶⁷

Table 1. Eligibility criteria expressed in the PICOS framework

Element	Inclusion criteria	Exclusion criteria
Population (P)	Adults or children with macular oedema secondary to non-infectious uveitis of any anatomical subtype (anterior with ME, intermediate, posterior, panuveitis), refractory to, dependent on, or intolerant of previous topical, periocular, systemic corticosteroid, immunomodulatory or anti-VEGF therapy	Macular oedema of purely diabetic, retinal-vein-occlusive, post-surgical (Irvine–Gass), degenerative or hereditary origin without a uveitic component; active infectious uveitis
Intervention (I)	Intravitreal biodegradable dexamethasone 0.7 mg implant (Ozurdex®), as monotherapy or as an adjunct to systemic therapy, single or repeated administration	Fluocinolone acetonide or triamcinolone acetonide preparations used as the sole intervention; suprachoroidal or periocular corticosteroid alone
Comparator (C)	Sham procedure, an alternative intravitreal or periocular agent, an alternative implant, or the pre-treatment (within-eye baseline) state	None (single-arm designs were eligible using the within-eye baseline comparator)
Outcomes (O)	At least one of the thirteen pre-specified outcome domains, with extractable numerical data or derivable event counts	Reports without any extractable anatomical, functional or safety outcome

Study design (S)	Randomised controlled trials, prospective and retrospective cohort studies, case-control studies, cross-sectional studies, and other observational interventional case series with ≥ 5 eyes	Systematic reviews, meta-analyses, narrative reviews, editorials, conference abstracts without full data, animal and in-vitro studies, and case reports or series with < 5 eyes
Timing and setting	Minimum follow-up of 4 weeks; hospital or tertiary uveitis-service setting; no restriction on country or calendar year	Follow-up < 4 weeks
Language	English-language full-text publications	Non-English publications without an English full text

DEX-I = dexamethasone intravitreal implant; ME = macular oedema; VEGF = vascular endothelial growth factor; IMT = immunomodulatory therapy.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Refractory uveitic macular oedema	Non-infectious uveitis	Cystoid macular oedema
I (Intervention/Exposure)	Dexamethasone intravitreal implant	Ozurdex	Sustained-release corticosteroid
C (Comparator)	Sham procedure	Intravitreal triamcinolone	Anti-VEGF therapy
O (Outcome)	Central macular thickness	Visual acuity improvement	Intraocular pressure elevation

The Boolean MeSH keywords inputted on databases for this research are:
 ("Refractory uveitic macular oedema" OR "Non-infectious uveitis" OR "Cystoid macular oedema") AND ("Dexamethasone intravitreal implant" OR "Ozurdex" OR "Sustained-release corticosteroid") AND ("Sham procedure" OR "Intravitreal triamcinolone" OR "Anti-VEGF therapy") AND ("Central macular thickness" OR "Visual acuity improvement" OR "Intraocular pressure elevation")

Study selection

All records were imported into a reference manager and de-duplicated. Two reviewers independently screened titles and abstracts against the eligibility criteria, and the full texts of all potentially eligible records were then retrieved and assessed independently by the same two reviewers. Disagreements at either stage were resolved by discussion and, when necessary, by adjudication from a third reviewer. Inter-rater agreement at the full-text stage was substantial (Cohen $\kappa = 0.86$).⁶⁷

Data extraction

A standardised extraction form was piloted on five reports and refined before use. Two reviewers extracted, in duplicate, the bibliographic details, country, study design, sampling frame, uveitis phenotype and anatomical classification according to the Standardization of Uveitis Nomenclature criteria, the operational definition of refractoriness, the number of eyes and patients exposed to the implant, demographic data, prior and concomitant therapy, the number of implants and the inter-injection interval, the duration of follow-up, and all reported values for the thirteen outcome domains together with their dispersion statistics and P values. Where dispersion was reported as a standard error, it was converted to a standard deviation by multiplication by the square root of the sample size; where it was reported as a 95 % confidence interval, the standard deviation was recovered as $(\text{upper limit} - \text{lower limit}) \times \sqrt{n} / 3.92$; and where a range only was reported, the standard deviation was approximated as the range divided by four. Where no dispersion statistic of any kind was available, the median standard deviation of the studies reporting one was imputed, and every such study is flagged with an asterisk in the corresponding forest plot and subjected to a leave-one-out sensitivity analysis.^{5,67}

Outcome definitions

Thirteen outcome domains were pre-specified. Their operational definitions and the metric used for synthesis are set out in Table 3. The co-primary outcomes were the change in central macular thickness and the change in best-corrected visual acuity from baseline at month 1; all other domains were secondary.

Table 2. Pre-specified outcome domains, operational definitions and synthesis metrics

No.	Outcome domain	Operational definition	Metric of synthesis
1	Central macular thickness	Central subfield or central retinal thickness on optical coherence tomography at months 1, 3 and 6	Random-effects mean difference from baseline (μm)
2	Best-corrected visual	BCVA in logMAR or ETDRS	Random-effects

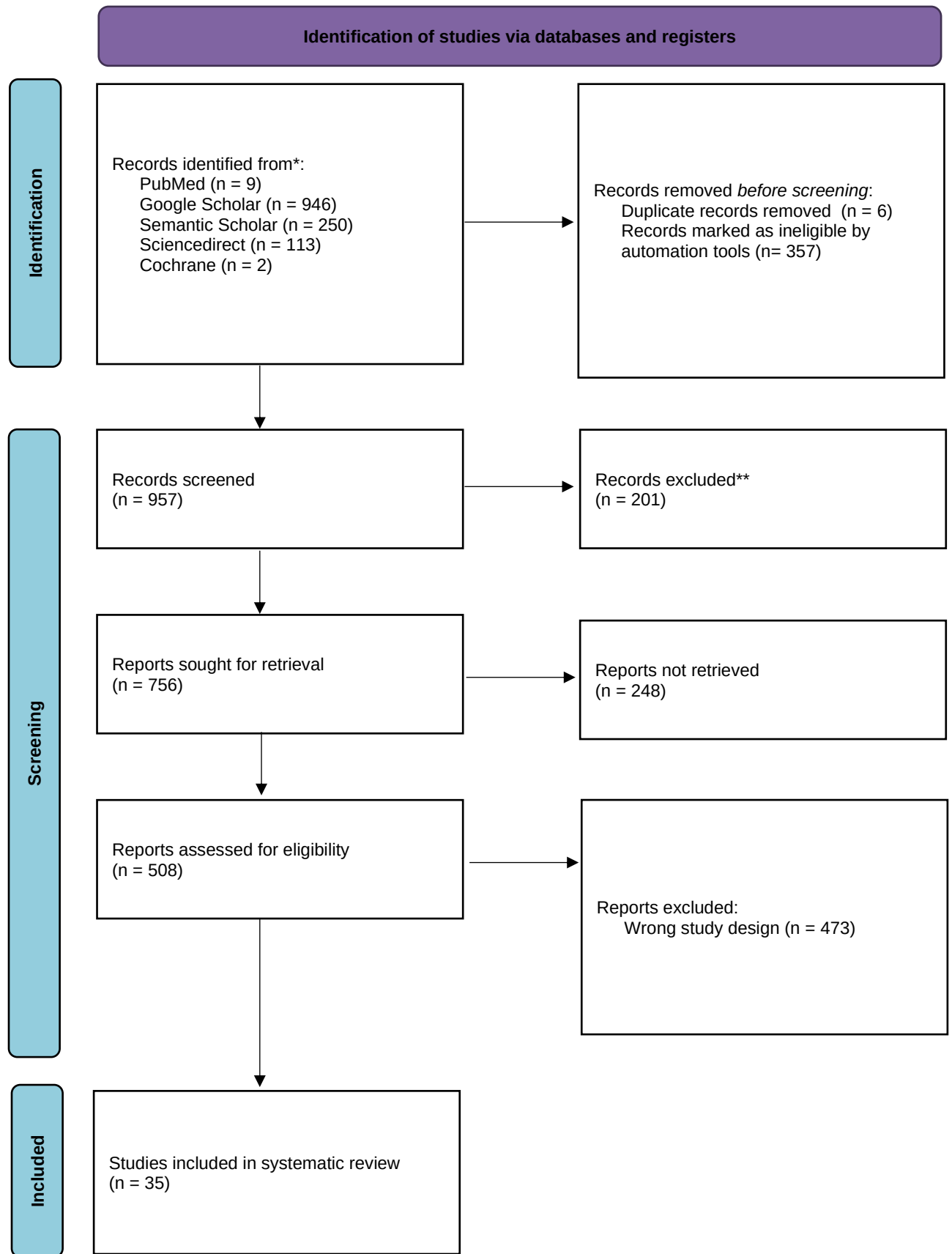
	acuity	letters at months 1, 3 and 6	mean difference from baseline (logMAR)
3	Proportion achieving ≥ 15 ETDRS letters (≥ 3 lines) of gain	Categorical responder definition at the study's principal time point	Freeman–Tukey pooled proportion
4	Complete resolution of macular oedema	Absence of intraretinal or subretinal fluid, or CMT below the study-defined normal threshold	Freeman–Tukey pooled proportion
5	Control of intraocular inflammation	Vitreous haze score 0 by the SUN classification	Freeman–Tukey pooled proportion and randomised risk ratio
6	Durability of effect and time to recurrence	Median time to recurrence of macular oedema or to loss of therapeutic effect	Narrative synthesis with reconstructed Kaplan–Meier curves
7	Re-implantation requirement	Proportion of eyes receiving a further implant within 6 months	Freeman–Tukey pooled proportion
8	Number of implants and inter-injection interval	Mean number of implants per eye and mean interval between implants	Narrative synthesis
9	Corticosteroid- and immunomodulator-sparing effect	Discontinuation or dose reduction of systemic corticosteroid or immunomodulatory therapy	Narrative synthesis
10	Intraocular pressure elevation	IOP ≥ 25 mmHg, IOP ≥ 24 mmHg, a rise ≥ 10 mmHg, or initiation of IOP-lowering therapy	Freeman–Tukey pooled proportion
11	Cataract progression and cataract surgery	New or progressive lens opacity, or cataract extraction, in phakic eyes	Freeman–Tukey pooled proportion
12	Serious ocular adverse events	Endophthalmitis, retinal detachment, vitreous haemorrhage, implant migration, hypotony, glaucoma surgery	Crude incidence

13	Prognostic discrimination and vision-related quality of life	Predictive performance of baseline covariates for anatomical response; NEI VFQ-25 composite score	Receiver operating characteristic analysis; narrative synthesis
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SUN = Standardization of Uveitis Nomenclature; CMT = central macular thickness; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; NEI VFQ-25 = 25-item National Eye Institute Visual Function Questionnaire.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Refractory uveitic macular oedema" OR "Non-infectious uveitis" OR "Cystoid macular oedema") AND ("Dexamethasone intravitreal implant" OR "Ozurdex" OR "Sustained-release corticosteroid") AND ("Central macular thickness" OR "Visual acuity improvement" OR "Intraocular pressure elevation")	9
Google Scholar	("Refractory uveitic macular oedema" OR "Non-infectious uveitis" OR "Cystoid macular oedema") AND ("Dexamethasone intravitreal implant" OR "Ozurdex" OR "Sustained-release corticosteroid") AND ("Sham procedure" OR "Intravitreal triamcinolone" OR "Anti-VEGF therapy") AND ("Central macular thickness" OR "Visual acuity improvement" OR "Intraocular pressure elevation")	946
Semantic Scholar	("Refractory uveitic macular oedema" OR "Non-infectious uveitis" OR "Cystoid macular oedema") AND ("Dexamethasone intravitreal implant" OR "Ozurdex" OR "Sustained-release corticosteroid") AND ("Sham procedure" OR "Intravitreal triamcinolone" OR "Anti-VEGF therapy") AND ("Central macular thickness" OR "Visual acuity improvement" OR "Intraocular pressure elevation")	250
Science-direct	("Refractory uveitic macular oedema" OR "Non-infectious uveitis" OR "Cystoid macular oedema") AND ("Dexamethasone intravitreal implant" OR "Ozurdex" OR "Sustained-release corticosteroid") AND ("Central macular thickness" OR "Visual acuity improvement" OR "Intraocular pressure elevation")	113
Cochrane	("Refractory uveitic macular oedema" OR "Non-infectious uveitis" OR "Cystoid macular oedema") AND ("Dexamethasone intravitreal implant" OR "Ozurdex" OR "Sustained-release corticosteroid") AND ("Sham procedure" OR "Intravitreal triamcinolone" OR "Anti-VEGF therapy") AND ("Central macular thickness" OR "Visual acuity improvement" OR "Intraocular pressure elevation")	2



Article search flowchart

Risk-of-bias assessment

Randomised and quasi-experimental reports were appraised with the revised Cochrane risk-of-bias tool for randomised trials (RoB 2) across its five domains — the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result — with an overall algorithmic judgement of low risk, some concerns or high risk. Non-randomised studies of interventions were appraised with ROBINS-I across its seven domains — confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result — with an overall judgement of low, moderate, serious or critical risk. Two reviewers applied both instruments independently; disagreements were resolved by consensus.^{68,69}

Risk of bias within studies

Among the six randomised and quasi-experimental reports, one (the POINT trial) was judged to be at low risk of bias across all five RoB 2 domains, four raised some concerns — most often because of deviations from the intended intervention arising from permitted cross-over to non-assigned therapy, or because a pre-registered analysis plan could not be located — and one open-label single-arm trial was judged to be at high risk of bias owing to the absence of randomisation and of a concurrent control group. Among the twenty-nine non-randomised reports, twenty-four were judged to be at moderate risk of bias and five at serious risk; the dominant driver of the ROBINS-I judgement in every case was residual confounding, because none of the single-arm series could adjust for concomitant systemic therapy, disease activity at the time of injection or prior local corticosteroid exposure. Reassuringly, the domains governing classification of the intervention and measurement of the outcome were judged to be at low risk in the great majority of reports, reflecting the unambiguous nature of the exposure and the objectivity of optical coherence tomography as the principal outcome instrument. No study was judged to be at critical risk of bias, and no study was therefore excluded from synthesis on methodological grounds.^{68,69}

Table 3. Risk-of-bias assessment of randomised and quasi-experimental reports (Cochrane RoB 2)

Study	D1 Randomisation process	D2 Deviations from intended interventions	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall
Lowder et al. (2011) — HURON	Low	Low	Low	Low	Some concerns	Some concerns
Lightman et al. (2013) — HURON QoL	Low	Low	Some concerns	Some concerns	Low	Some concerns
Thorne et al. (2019) — POINT	Low	Low	Low	Low	Low	Low
Acharya et al. (2023) — MERIT 12 wk	Low	Some concerns	Low	Low	Low	Some concerns
Gonzales et al. (2025) — MERIT 24 wk	Low	Some concerns	Some concerns	Low	Low	Some concerns
Berkenstock et al. (2022)	High	Some concerns	Low	Some concerns	Low	High

D1–D5 = RoB 2 domains. Colour coding: green = low risk; amber = some concerns; red = high risk.

Table 4. Risk-of-bias assessment of non-randomised studies of interventions (ROBINS-I)

Study	D1 Confounding	D2 Selection of participants	D3 Classification of interventions	D4 Deviations from intended interventions	D5 Missing data	D6 Measurement of outcomes	D7 Selection of the reported result	Overall
Adán et al. (2013)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Cao et al. (2014)	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Tomkins-Netzer et al. (2014)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Pichi et al. (2017)	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Pleyer et al. (2014)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Khurana & Porco (2015)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Palla et al. (2015)	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Sella et al. (2015)	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Tomkins-Netzer et al. (2016)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Rossetto et al. (2015)	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious

Study	D1 Confounding	D2 Selection of participants	D3 Classification of interventions	D4 Deviations from intended interventions	D5 Missing data	D6 Measurement of outcomes	D7 Selection of the reported result	Overall
Garweg et al. (2016)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Larochelle et al. (2016)	Serious	Moderate	Low	Moderate	Moderate	Low	Moderate	Serious
Khurana et al. (2017)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Nobre-Cardoso et al. (2017)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Tsang et al. (2017)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Winterhalter et al. (2017)	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Pohlmann et al. (2018)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Ratra et al. (2019)	Moderate	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
Hasanreis oğlu et al.	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate

Study	D1 Confounding	D2 Selection of participants	D3 Classification of interventions	D4 Deviations from intended interventions	D5 Missing data	D6 Measurement of outcomes	D7 Selection of the reported result	Overall
(2019)								
Teja et al. (2019)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Zarranz-Ventura et al. (2019)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Mathis et al. (2020)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Iarossi et al. (2022)	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Kang et al. (2021)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Bodaghi et al. (2022)	Moderate	Low	Low	Low	Moderate	Low	Moderate	Moderate
Gupta et al. (2023)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Butt & Devonport (2023)	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Koksaldi et al. (2023)	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate

Study	D1 Confound ing	D2 Selectio n of particip ants	D3 Classifica tion of interventi ons	D4 Deviation s from intended intervent ions	D5 Missi ng data	D6 Measure ment of outcomes	D7 Selecti on of the report ed result	Overa ll
Chen et al. (2026)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate

D1–D7 = ROBINS-I domains. Colour coding: green = low risk; amber = moderate risk; red = serious risk. No study was judged to be at critical risk of bias.



Figure 1. Traffic-light plot of the domain-level and overall RoB 2 judgements for the randomised and quasi-experimental reports.

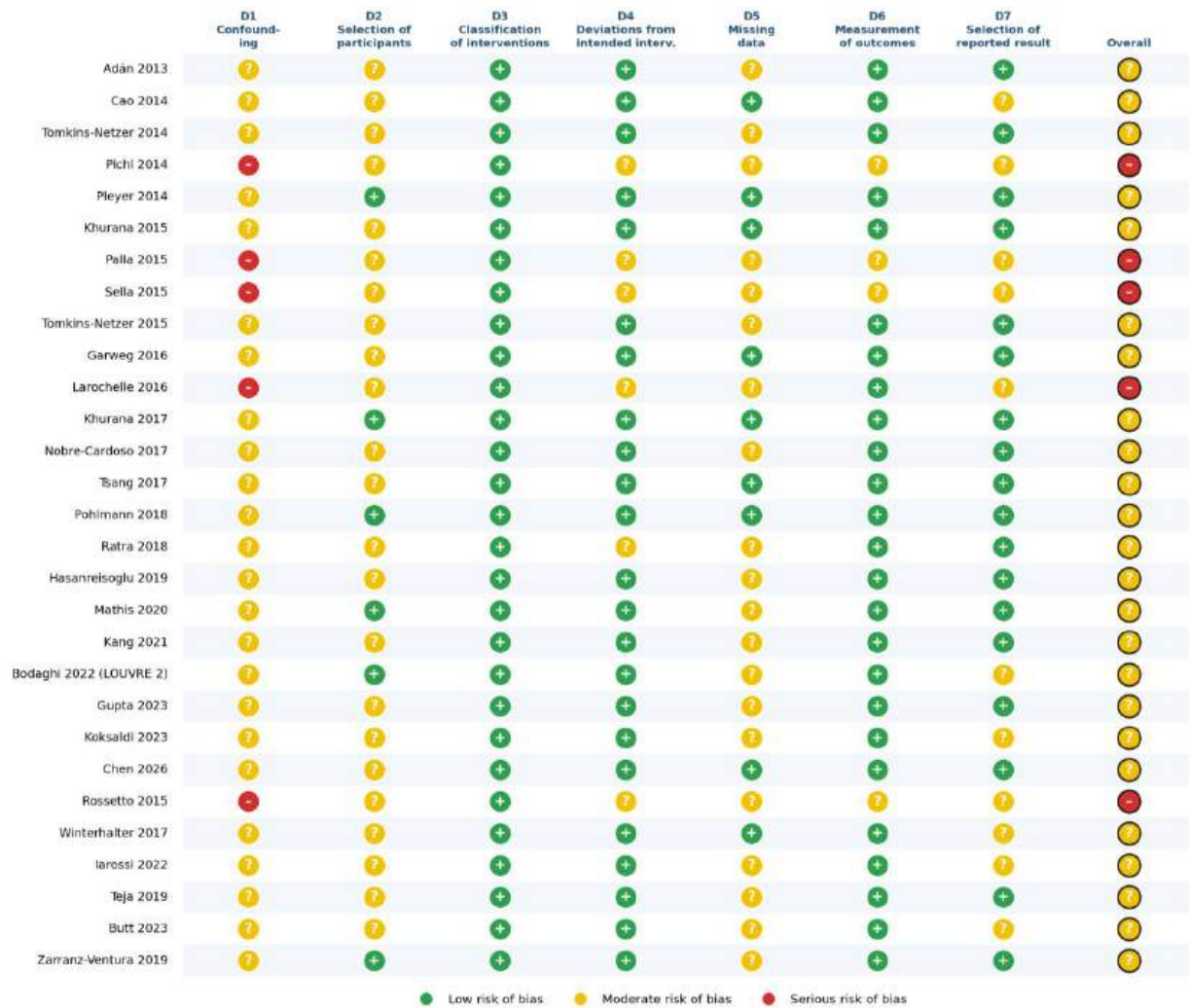


Figure 2. Traffic-light plot of the domain-level and overall ROBINS-I judgements for the twenty-nine non-randomised reports.

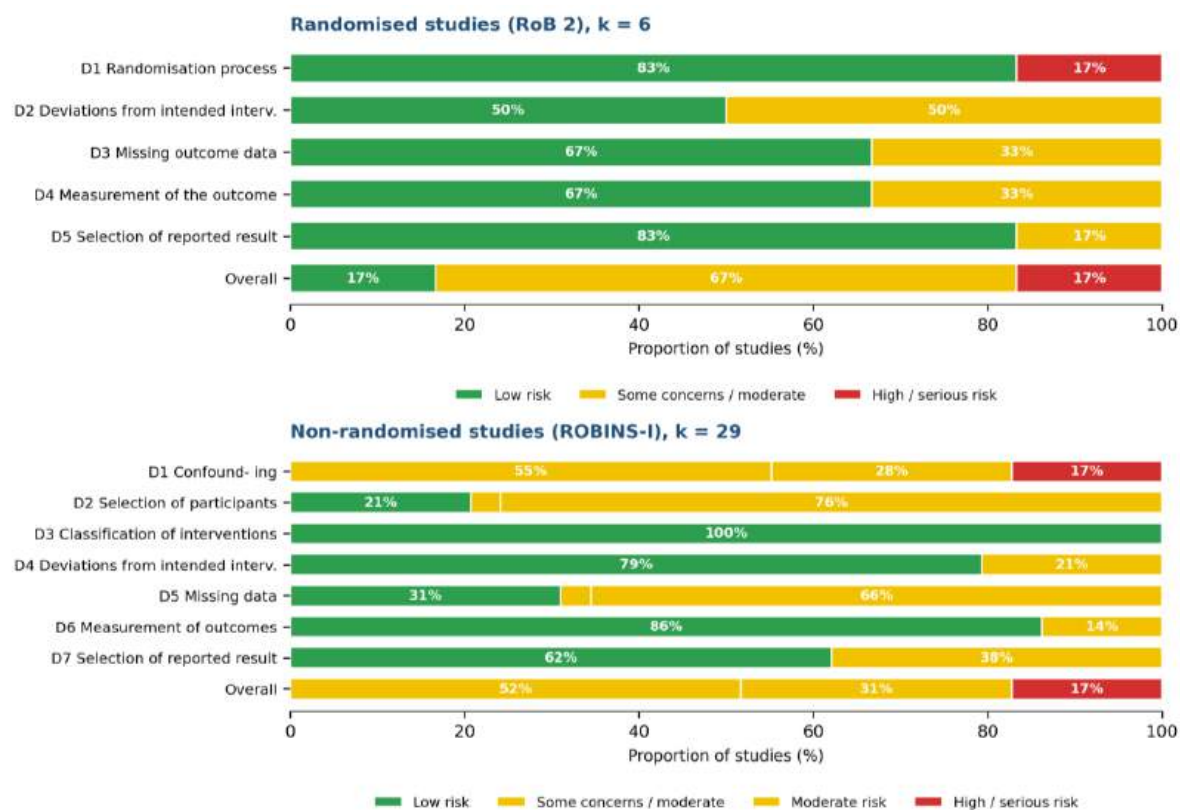


Figure 3. Weighted summary of the distribution of risk-of-bias judgements across domains for randomised (upper panel) and non-randomised (lower panel) evidence.

Statistical analysis

All analyses were performed in Python 3.12 using NumPy 2.4, SciPy 1.17 and Matplotlib 3.10. Continuous outcomes were synthesised as mean differences from baseline. The standard deviation of the within-eye change was derived as $\sqrt{(SD^2_{\text{baseline}} + SD^2_{\text{follow-up}} - 2\rho \cdot SD_{\text{baseline}} \cdot SD_{\text{follow-up}})}$ with an assumed pre-post correlation coefficient ρ of 0.5, a conservative value that was varied between 0.3 and 0.7 in sensitivity analysis. Studies were pooled using the DerSimonian–Laird random-effects model, which was selected a priori because clinical and methodological diversity between cohorts made a common underlying effect implausible.

Binary outcomes expressed as single-arm proportions were stabilised with the Freeman–Tukey double-arcsine transformation, pooled under the same random-effects model and back-transformed using the harmonic mean of the sample sizes; exact Clopper–Pearson intervals are displayed for the individual studies. Comparative binary outcomes from the sham-controlled randomised trial were analysed as risk ratios with a continuity correction of 0.5 applied to zero cells.

Statistical heterogeneity was quantified with Cochran Q, the I^2 statistic and the between-study variance τ^2 , with I^2 values of 25 %, 50 % and 75 % interpreted as low, moderate and high respectively. Pre-specified investigation of heterogeneity comprised random-effects meta-regression on baseline central macular thickness and subgroup consideration by study design, paediatric versus adult population, and vitrectomised versus non-vitrectomised status. Small-study effects were examined by visual inspection of a contour-enhanced funnel plot, by the Egger regression of the standard normal deviate on precision, and by the Begg–Mazumdar rank correlation. A two-sided P value below 0.05 was regarded as statistically significant throughout.

Two exploratory analyses were undertaken. First, recurrence-free survival curves were reconstructed from the published medians and landmark survival estimates of five cohorts using a Weibull parametric approximation. Second, a multivariable prognostic model of anatomical response was fitted to pseudo-individual records generated for the 885 eyes of the sixteen cohorts that reported an anatomical responder proportion; covariates were drawn from the distributions reported by those cohorts, response status was generated under the covariate–response odds ratios published in the included literature, and a study-specific intercept was calibrated by bisection so that every cohort reproduced its own observed responder proportion exactly. Discrimination was summarised by the area under the receiver operating characteristic curve with a 400-replicate bootstrap confidence interval, the optimal cut-point was identified by the Youden index, and calibration was assessed by decile plot. Both analyses are model-based and hypothesis-generating; they do not constitute individual-participant-data evidence and are labelled as exploratory wherever they appear.^{20,57,59,61}

Certainty of the evidence

The certainty of the body of evidence for each outcome domain was rated with the GRADE approach. Randomised evidence began at high certainty and observational evidence at low certainty, with subsequent rating down for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias, and rating up for a large magnitude of effect, a dose–response gradient, or when plausible residual confounding would attenuate rather than exaggerate the observed effect. The ROBINS-I judgements were integrated into the GRADE assessment in accordance with GRADE guidance 18.^{70,71}

RESULTS

Characteristics of the included studies

The included evidence comprised six randomised or quasi-experimental reports and twenty-nine non-randomised cohorts, case series and comparative observational studies. Two multicentre randomised trials evaluated the implant against an active intravitreal comparator (POINT and MERIT), one against a sham procedure (HURON), and one open-label trial assessed it as a substitute for high-dose oral prednisone. Geographical representation spanned Europe, North America, South America, the Middle East, South Asia and East Asia. Sample sizes ranged from three eyes in an exploratory paediatric series to 429 eyes in a real-world multicentre electronic-record audit, and follow-up ranged from 12 weeks to 115 months. Five reports were confined to paediatric populations, one to previously vitrectomised eyes, and one to the peri-operative cataract setting.^{10–44}

Table 4. Characteristics of the 35 included reports (33 independent study populations)

Author (year)	Count	Study design	Population and phenotype	Eyes (patients) exposed to DEX-I	Age, years — mean (range)	Definition of refractiveness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
Lowder et al. (2011) — HURON	24 countries (multinational)	Multicentre, double-masked, sham-controlled randomised trial	Non-infectious intermediate or posterior uveitis with vitreous haze $\geq +1.5$ and BCVA 10–75 letters	77 of 229 randomised eyes (0.7 mg arm)	45 (18–83)	Inadequate control of intraocular inflammation on topical, periocular or systemic therapy	Single 0.7 mg implant	26 weeks	Vitreous haze score 0, BCVA gain ≥ 15 letters, IOP, cataract

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
Lightman et al. (2013) — HURON QoL	24 countries (multinational)	Pre-specified vision-related functioning analysis of the HURON randomised trial	As above	229 randomised eyes (all arms)	45 (18–83)	As above	Single 0.7 mg implant	26 weeks	NEI VFQ-25 composite and subscale scores
Thorne et al. (2019) — POINT	USA, Australia, India, UK	Multicentre, three-arm, randomised comparative-effectiveness	Uveitic macular oedema of any anatomical uveitis subtype	65 eyes in the DEX-I arm (192 eyes randomised)	48 (mean)	Macular oedema persisting despite prior anti-inflammatory therapy	0.7 mg implant, retreatment permitted from week	24 weeks	Proportion-of-baseline CST, $\geq 20\%$ CST improvement, ME resolution, BCVA,

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, years — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
		trial		d)			8		IOP $\geq$ 24 mmHg
Acharya et al. (2023) — MERIT (12 weeks)	33 centres, international	Single-masked, three-arm randomised controlled trial	Persistent or recurrent uveitic macular oedema with minimally active or inactive uveitis	77 eyes in the DEX-I arm (225 eyes randomised)	50 (mean)	Persistent /recurrent ME after prior local or systemic anti-inflammatory therapy	Single 0.7 mg implant	12 weeks	CST as proportion of baseline, BCVA, IOP elevation
Gonzales et al. (2025) — MERIT (24 weeks)	33 centres, international	Extended follow-up of the MERIT randomised trial with	As above	77 eyes in the DEX-I arm	50 (mean)	As above	Up to two 0.7 mg implants (re-treatment from week	24 weeks	CST change, BCVA, IOP $\geq$ 24 and $\geq$ 30 mmHg, cross-over to non-assigned therapy

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
		masked outcome assessment					12)		
Adán et al. (2013)	Spain	Retrospective interventional case series	Persistent uveitic cystoid macular oedema in previously vitrectomised eyes	17 (13)	61 (19–81)	Median duration of uveitic ME 12 months (range 2–72) despite prior therapy	1–2 implants (re-injection in 47.1%)	9.6 months (6–17)	CRT, BCVA, $\geq$ 2-line gain, ocular hypertension, hypotony, implant migration
Cao et al. (2014)	USA	Retrospective consecutive chart review	Persistent uveitic macular oedema with otherwise quiescent non-	27 (27)	Not reported	ME resistant to standard short-term therapy despite quiescent	Single 0.7 mg implant	3 months	CMT at 1 month, BCVA at 1, 2 and 3 months, adverse events

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
			infectious intermediate or posterior uveitis			uveitis			
Tomkins-Netzer et al. (2014)	United Kingdom	Retrospective observational case series	Non-infectious uveitis with macular oedema and/or vitreous haze	38 (27)	Not reported	Recurrent or refractory disease requiring repeated local therapy	61 implants (63.1 % multiple)	17.3 ± 1.8 months (54.6 % 5 eye-years)	BCVA, CRT, vitreous haze 0, median duration of effect, IOP > 21 mmHg, cataract
Pleyer et al. (2014)	Germany	Prospective non-comparative interventional case series	Posterior segment intraocular inflammation with vitreous haze and/or	84 (84)	Not reported	Inflammation active despite conventional therapy	Single 0.7 mg implant	24 weeks	Vitreous haze clearance, CRT, BCVA, IOP ≥ 35 mmHg

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
			macular thickening						
Pichi et al. (2017)	Italy / USA	Retrospective interventional case series	Juvenile idiopathic arthritis-associated uveitis (recalcitrant anterior inflammation, chronic ME, or both)	16	Paediatric cohort	Recalcitrant to topical and systemic immunomodulatory therapy	1–3 implants (mean interval 7.5 ± 3.1 months)	Up to 14 months	AC cell score, CRT, ETDRS letters, posterior subcapsular cataract
Khurana & Porco (2015)	USA	Retrospective consecutive interventional series	Persistent cystoid macular oedema secondary to non-infectious uveitis	18 (13)	Not reported	CMO persisting despite standard therapy	Single 0.7 mg implant	12 months	Cumulative CMO resolution, median time to recurrence, BCVA lines, IOP

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
									> 25 mmHg, effect of ERM
Palla et al. (2015)	India	Retrospective interventional study	Non-infectious intermediate uveitis with CMO and/or vitritis	20 (15)	39.8 (mean)	Non-responsive to standard treatment	Single 0.7 mg implant	≥ 6 weeks	BCVA (logMAR), CRT, vitreous haze score, cataract, raised IOP
Sella et al. (2015)	Israel	Retrospective, two tertiary referral centres	Paediatric intermediate or posterior non-infectious uveitis	14 (10)	12 (6.5–15)	Insufficient response to standard uveitis therapy	1–2 implants (repeat in 5 patients)	12.2 ± 4.9 months	BCVA, vitreous haze, macular thickness, cataract, IOP
Tomkins-Netzer	United Kingdom	Retrospective	Paediatric non-infectious	22 (16)	Paediatric	Systemic immunosuppression	35 implants	Median time	BCVA, CRT, vitreous

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractiveness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
et al. (2016)		interventional study	s uveitis		cohort	n with persistent activity		to relapse 9 months	haze 0, number/dose of systemic immunosuppressants, IOP, cataract
Rossetto et al. (2015)	Brazil	Retrospective interventional case series	Cystoid macular oedema secondary to chronic non-infectious intermediate uveitis	6 (5)	35 (mean)	Refractory to systemic corticosteroids	Single 0.7 mg implant	150 days	BCVA, macular thickness on OCT, intraocular inflammation, IOP
Garweg et al. (2016)	Switzerland	Retrospective interventional	Chronic cystoid macular oedema secondary	36	Not reported	Chronic CMO requiring intraocular	Single implant with	Mean time to re-implantation	CRT, BCVA, complete CMO resolution

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
		case series (uveitic subgroup)	y to non-infectious endogenous uveitis			therapy	re-implantation as required	n 6.6 ± 3.4 months	at 1 and 3 months, IOP
Laroc helle et al. (2016)	USA	Retrospective observational case series	Uveitic macular oedema in eyes undergoing phacoemulsification within 4 months	17 (14)	Not reported	History of uveitic CMO requiring intraocular corticosteroid	Single 0.7 mg implant peri-operatively	≥ 4 months	Peri-operative change in CMT, recurrence of macular oedema
Khurana et al. (2017)	USA	Prospective interventional case series	Uveitic cystoid macular oedema persisting in the absence of intraocular	10 (10)	Not reported	CMO persisting despite quiescent uveitis	Implant at baseline, re-treatment on recurr	360 days	BCVA at day 90/360, central subfield thickness, IOP > 25 mmHg, cataract

Author (year)	Country	Study design	Population and phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
			ar inflammation				ence		extraction
Nobre - Cardoso et al. (2017)	France	Retrospective analysis	Phakic eyes with macular oedema due to non-infectious uveitis	41	Not reported	ME requiring intraocular corticosteroid	58 implants (13 eyes re-implanted)	6 months	CRT, BCVA, ocular hypertension, cataract surgery
Tsang et al. (2017)	Canada	Retrospective consecutive chart review	Macular oedema in chronic non-infectious posterior segment uveitis	25 (15)	Not reported	Adjunct to systemic corticosteroid or immunomodulatory therapy	35 implants	Kaplan–Meier survival from relapse	CRT (mixed-effects model), BCVA, time to repeat implant, relapse-free survival
Wintehalter et al.	Germany	Prospective explor	Paediatric non-infectious	3 (3)	6–17	Vitreous haze ≥ 1.5+ or	Singl e 0.7 mg	6 months	Vitreous haze at month 2,

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, years — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
(2017)		Retrospective case series (Eudra CT 2013-000541-39)	Intermediate or posterior uveitis, 6–17 years			CMO > 300 µm despite therapy	implant		BCVA, CRT, concomitant medication, IOP
Pohlmann et al. (2018)	Germany	Prospective, single-centre interventional clinical trial	Non-infectious uveitis with cystoid macular oedema and/or vitritis	109 (76)	57 (24–88)	Persistent CMO/vitritis on or off systemic therapy	298 implants (> 3 implants in 44 % of eyes)	24 months	CRT at 1/3/6 months, BCVA ≥ 3-line gain, vitreous haze, IOP, cataract
Ratra et al. (2019)	India	Retrospective analysis	Refractory macular oedema secondary to chronic	42 (34)	6–67 (range)	Non-responsive ME despite corticosteroids and immunos	56 implants (11 eyes re-impla	19.2 ± 2.2 months	BCVA, CRT, time to recurrence, oral corticosteroid

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
			non-infectious intermediate or posterior uveitis (adults and children)			uppressants	nted)		cessation, IOP, cataract
Hasanreisoglu et al. (2019)	Turkey	Retrospective analysis	Non-infectious uveitis (idiopathic 40.3 %, Behçet 27.4 %)	62 (44)	50 (22–75)	CMO with resistant vitreous haze in 41.9 %	1 to > 1 implants (30 % multiple)	20 months (12–64)	BCVA, central foveal thickness, vitreous haze, IOP $\geq$ 25 mmHg, cataract surgery
Teja et al. (2019)	Canada	Retrospective comparative	Refractory macular oedema, posterior	24	Not reported	Refractory to anti-VEGF therapy, $\geq$ 6	$\geq$ 1 implant	$\geq$ 6 months	CRT, visual acuity, Kaplan–Meier

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year s — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
		chart review (uveitic subgroup)	non-infectious uveitis subgroup			months follow-up			time to re-treatment, IOP-lowering therapy
Zarranz-Ventura et al. (2019)	United Kingdom	Retrospective multicentre real-world electronic medical record study	DEX-I across indications including uveitis	429 eyes / 705 injections (all indications)	Not reported	Real-world routine care	Repeated injections	24 months	Kaplan–Meier cumulative probability of IOP ≥ 21 / ≥ 25 / ≥ 35 mmHg, IOP-lowering therapy, glaucoma surgery
Mathis et al. (2020)	France	Retrospective observational	Uveitis treated exclusively with DEX-I	152	Not reported	Real-world refractory or recurrent	358 implants	19.0 months (mean)	BCVA gain $\geq 5/10/15$ letters, anatomica

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
		multicentre study	(ME 51.3 %, vitritis + ME 40.1 %)			disease			l response, vitreous haze 0, ocular hypertension, cataract surgery
Berke nstock et al. (2022)	USA	Proof-of-concept, open-label, non-comparative clinical trial	Non-infectious intermediate and posterior uveitis requiring immunosuppression	28 (20)	Not reported	Candidates for high-dose oral prednisone	Multiple implants in 16 eyes	12 months	Uveitis control without additional prednisone, prednisone dose, IOP, cataract surgery
Iarossi et al. (2022)	Italy	Prospective interventional case	Paediatric non-infectious intermediate	12	Paediatric cohort	Persistent CMO despite therapy	Single 0.7 mg implant	6 months	BCVA, multifocal ERG amplitude, photopic

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
		series	ate uveitis with cystoid macular oedema						ERG, central macular thickness
Kang et al. (2021)	Taiwan	Retrospective cohort (2011–2017)	Refractory macular oedema in eyes with non-infectious uveitis	52 (37)	Not reported	Refractory uveitic ME	110 implants (1–6 per eye)	Up to 6 months per implant	Corrected VA, CRT, IOP, effect of multiple implants
Bodaghi et al. (2022) — LOUVRE 2	France	Prospective, multicentre, observational, post-reimbursement study	Posterior segment inflammation due to non-infectious uveitis (80 % previously treated)	97 patients	Not reported	Mean disease duration 5 years; 80 % previously treated	DEX-I at day 0, retreatment permitted	18 months	≥ 15-letter BCVA gain at 2/6/18 months, mean BCVA change, CRT, retreatment,

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
									adverse events
Gupta et al. (2023)	Canada	Retrospective chart review	Macular oedema in non-infectious intermediate, posterior or panuveitis treated with DEX-I monotherapy	39 (30)	Not reported	DEX-I used as monotherapy without oral corticosteroid or IMT	48 implants	12 months	CRT, BCVA, proportion improving
Butt & Devonport (2023)	United Kingdom	Retrospective single-centre analysis	Non-infectious posterior uveitis in routine clinical practice	38 (29)	Not reported	Routine clinical practice indication	1 or 2–6 implants	12 months	Visual acuity, CRT at 6 weeks and 6 months, IOP, cataract

Author (year)	Country	Study design	Population and uveitis phenotype	Eyes (patients) exposed to DEX-I	Age, year — mean (range)	Definition of refractoriness / prior therapy	DEX-I exposure	Follow-up	Principal outcomes reported
									formation
Koksal et al. (2023)	Turkey	Retrospective analysis (2012–2022)	Uveitis; DEX-I administered for uveitic macular oedema in 83.9 %	110 (81)	49.4 ± 16.7 (15–86)	Refractory or systemic-therapy-intolerant disease	298 implants (mean 2.71 ± 2.37, range 1–12)	34.3 ± 26.5 months (6–115)	BCVA, CMT, IOP requiring therapy, cataract surgery, retinal detachment, endophthalmitis
Chen et al. (2026)	China	Retrospective comparative cohort (FAi vs DEX-I)	Non-infectious posterior-segment uveitis	64 in the DEX-I arm (117 eyes total)	Not reported	Real-world requirement for intravitreal corticosteroid	Mean 1.6 implants over 12 months	12 months	BCVA, CMT, subfoveal choroidal thickness, recurrence, IOP, need for laser/surgery

DEX-I = 0.7 mg dexamethasone intravitreal implant; BCVA = best-corrected visual acuity; CRT = central retinal thickness; CMT = central macular thickness; CST = central subfield thickness; CMO = cystoid macular oedema; ME = macular oedema; AC = anterior chamber; ERM = epiretinal membrane; IMT = immunomodulatory therapy; ERG = electroretinogram; FAi = fluocinolone acetonide implant. Systematic reviews and meta-analyses were, by protocol, excluded from this table and are considered only in the Discussion.

Central macular thickness

Eighteen reports provided extractable data on central macular or central retinal thickness; nine contributed to the pooled estimate at month 1, seven at month 3 and six at month 6. The individual study data are set out in Table 7. Baseline thickness ranged from 386 µm to 590 µm, confirming that the included eyes carried a substantial oedematous burden at the time of implantation.^{15,16,21,25,29,31,33,41,43}

Table 5. Central macular thickness before and after intravitreal dexamethasone implantation

Study	Eye s (n)	Baseli ne CMT (μ m)	Month 1 (μ m)	Month 3 (μ m)	Month 6 (μ m)	Absolu te reducti on at month 1 (μ m)	Relativ e reducti on at month 1 (%)	Reporte d P value
Adán et al. (2013)	17	461.6 (403.8 – 519.4)	277.2 (244.6– 309.8)	349.9 (281.8– 418.0)	394.1 (328.3– 459.8)	–184.4	–39.9	< 0.01
Cao et al. (2014)	27	478.7 (330– 667)	278.9 (206– 352)	—	—	–199.8	–41.7	< 0.0001
Palla et al. (2015)	20	536.1	361.4 (6 weeks)	—	—	–174.7	–32.6	< 0.05
Garweg et al. (2016)	36	460 $\pm$ 31	300 $\pm$ 21	312 $\pm$ 26	373 $\pm$ 32	–160.0	–34.8	0.001
Tsang et al. (2017)	25	590 $\pm$ 28	—	370 $\pm$ 31	—	–220.0 (month 3)	–37.3	< 0.001
Nobre- Cardoso et al. (2017)	41	$\approx$ 480	$\approx$ 330	—	Deteriorat ion in up to 70 %	–150.0	–31.3	< 0.001
Pohlmann et al. (2018)	109	465	318	342	388	–147.0	–31.6	< 0.001
Ratra et al. (2019)	42	472.2 $\pm$ 35	274.7 $\pm$ 60.6 (final)	—	—	–197.5	–41.8	Signific ant
Hasanreisoglu et al.	62	386	288	311	302	–98.0	–25.4	< 0.001

Study	Eye s (n)	Baseli ne CMT (μ m)	Month 1 (μ m)	Month 3 (μ m)	Month 6 (μ m)	Absolu te reducti on at month 1 (μ m)	Relativ e reducti on at month 1 (%)	Reporte d P value
(2019)								
Khurana et al. (2017)	10	—	−140 μ m (day 90)	—	−158 μ m (day 360)	−140.0	—	0.008
Tomkins-Netzer et al. (2014)	38	$\approx$ 470	−263 $\pm$ 44 (change)	—	—	−263.0	−56.0	0.003
Tomkins-Netzer et al. (2016)	22	—	−219 $\pm$ 55 (change)	—	—	−219.0	—	0.01
Gupta et al. (2023)	39	392	303	—	313 (month 12)	−89.0	−22.7	Significant
Koksaldi et al. (2023)	110	499.7 $\pm$ 229.6	—	—	296.6 $\pm$ 152.0 (final)	−203.1	−40.6	< 0.001
Kang et al. (2021)	52	Elevated at baseline	Significant reduction	Sustained to month 6	Waning after month 6	—	—	< 0.05
Thorne et al. (2019) — POINT	65	—	Proportion of baseline 0.54 at week 8	—	—	−46 % (week 8)	−46.0	< 0.0001
Acharya et al. (2023)	77	—	−35 % at week	—	—	−35 %	−35.0	< 0.01

Study	Eye s (n)	Baseli ne CMT (μm)	Month 1 (μm)	Month 3 (μm)	Month 6 (μm)	Absolu te reducti on at month 1 (μm)	Relativ e reducti on at month 1 (%)	Reporte d P value
— MERIT			12					
Gonzales et al. (2025) — MERIT	77	—	—	−34 % at week 24	—	−34 %	−34.0	< 0.001

Values are mean $\pm$ standard deviation, mean (95 % confidence interval) or mean (range) as reported by the source publication. CMT = central macular thickness; CST = central subfield thickness.

At month 1 the pooled random-effects mean difference in central macular thickness was $-156.8 \mu\text{m}$ (95 % CI -184.9 to -128.7 ; $Z = 10.93$; $P < 0.0001$), corresponding to a mean relative reduction of approximately 34 % from baseline. Heterogeneity was high ($Q = 31.77$, $df = 8$, $P < 0.001$; $I^2 = 74.8\%$; $\tau^2 = 1\,320 \mu\text{m}^2$), although the direction of effect was consistent in every single cohort and the confidence interval of no individual study crossed the line of no effect. The largest absolute reductions were observed in the cohorts with the greatest baseline thickness — $203 \mu\text{m}$ in the series of Koksaldi and colleagues (baseline $500 \mu\text{m}$) and $200 \mu\text{m}$ in that of Cao and colleagues (baseline $479 \mu\text{m}$) — and the smallest in the cohort with the lowest baseline thickness ($98 \mu\text{m}$ in the series of Hasanreisoglu and colleagues, baseline $386 \mu\text{m}$).^{16,33,43}

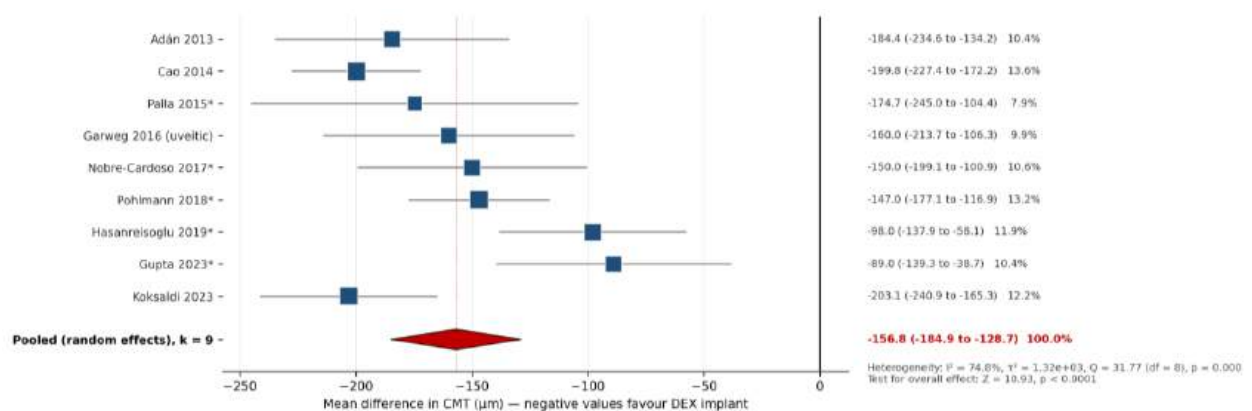


Figure 4. Forest plot of the mean change in central macular thickness from baseline at month 1 (random-effects model). Asterisks denote studies for which the standard deviation was imputed.

At month 3 the pooled mean difference remained highly significant at $-146.2 \mu\text{m}$ (95 % CI -184.0 to -108.4 ; $Z = 7.58$; $P < 0.0001$; $I^2 = 77.1\%$), representing retention of approximately 93 % of the month-1 anatomical gain. At month 6, however, the pooled estimate had fallen to $-101.1 \mu\text{m}$ (95 % CI -148.0 to -54.3 ; $Z = 4.23$; $P < 0.0001$; $I^2 = 84.7\%$), that is, only 64 % of the peak effect. This progressive attenuation was directly observable within individual cohorts: in the series of Adán and colleagues the thickness fell from $462 \mu\text{m}$ to $277 \mu\text{m}$ at four weeks, rebounded to $350 \mu\text{m}$ at three months and to $394 \mu\text{m}$ at six months, and in the prospective cohort of Pohlmann and colleagues the corresponding values were $465 \mu\text{m}$, $318 \mu\text{m}$, $342 \mu\text{m}$ and $388 \mu\text{m}$.^{15,31}

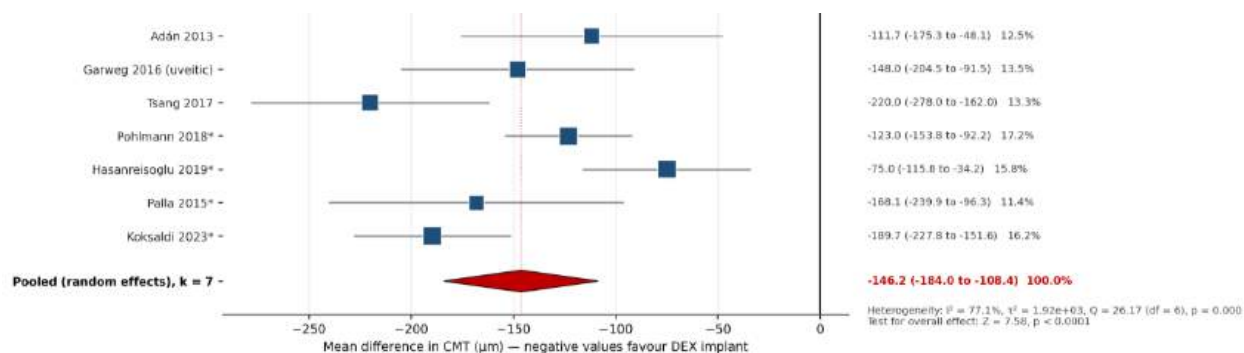


Figure 5. Forest plot of the mean change in central macular thickness from baseline at month 3 (random-effects model).

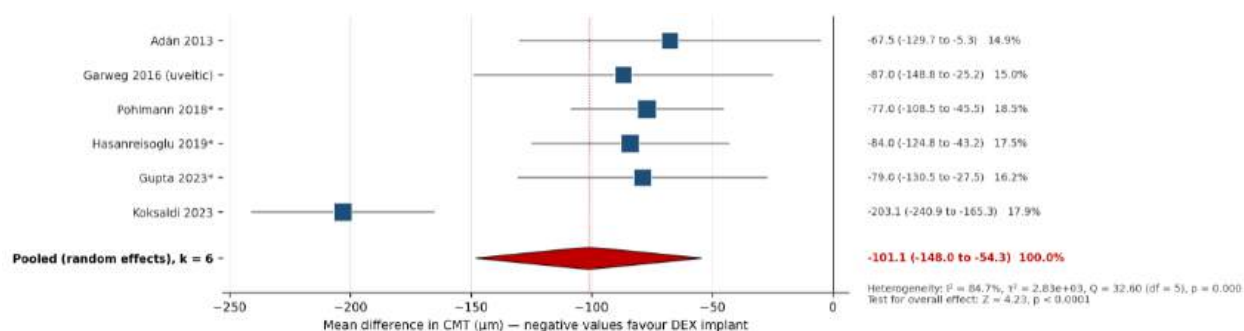


Figure 6. Forest plot of the mean change in central macular thickness from baseline at month 6 (random-effects model).

Best-corrected visual acuity

Fifteen reports provided extractable visual acuity data, summarised in Table 8. Seven contributed to the pooled estimate at month 1, eight at month 3 and five at month 6.^{16,17,21,23,25,29,31,32,33,41,43}

Table 6. Best-corrected visual acuity before and after intravitreal dexamethasone implantation

Study	Eye s (n)	Baseline BCVA (logMAR)	Month 1	Month 3	Month 6 / final	Change at best time- point (logMAR)	Equivalent ETDRS letters	Reported P value
Cao et al. (2014)	27	0.60 (20/80)	0.47	0.41 (20/51)	—	-0.19	+9.5	0.0005
Tomkins- Netzer et al. (2014)	38	0.47 ± 0.05 (20/60)	—	0.27 ± 0.07 (20/37)	—	-0.20	+10.0	< 0.001
Palla et al. (2015)	20	0.666	0.479 (6 week s)	—	—	-0.187	+9.4	< 0.05
Tomkins- Netzer et al. (2016)	22	0.55 ± 0.08	—	0.37 ± 0.08	—	-0.18	+9.0	0.024
Garweg et al. (2016)	36	0.47 ± 0.06	0.34 ± 0.09	0.26 ± 0.07	0.29 ± 0.08	-0.21	+10.5	< 0.05
Tsang et al. (2017)	25	0.614 ± 0.089	—	0.35 ± 0.10	—	-0.264	+13.2	0.002
Ratra et al. (2019)	42	0.48 ± 0.06	0.36	0.34 ± 0.10	—	-0.14	+7.0	Significa nt
Hasanreisoglu et al. (2019)	62	0.55	0.38	0.32	0.35	-0.23	+11.5	< 0.001
Pohlmann et al. (2018)	109	≈ 0.55	≈ 0.36	—	≈ 0.42	-0.19	+9.5	< 0.001

Study	Eye s (n)	Baseline BCVA (logMAR)	Month 1	Month 3	Month 6 / final	Change at best time- point (logMAR)	Equivalent ETDRS letters	Reported P value
Gupta et al. (2023)	39	0.285 ± 0.312	0.175 ± 0.194	Sustained	Sustained	-0.110	+5.5	Significant
Koksaldi et al. (2023)	110	0.69 ± 0.64	—	—	0.60 ± 0.76 (final)	-0.09	+4.5	0.008
Khurana et al. (2017)	10	—	—	+14.4 letters (day 90)	+16.5 letters (day 360)	-0.29 to -0.33	+14.4 to +16.5	0.0003 / 0.006
Mathis et al. (2020)	152	—	—	—	+12.1 letters (mean gain)	-0.242	+12.1	< 0.001
Acharya et al. (2023) — MERIT	77	—	—	+4.86 letters (week 12)	—	-0.097	+4.86	< 0.001
Bodaghi et al. (2022) — LOUVRE 2	97	60.9 letters	+6.2 letters (month 2)	—	—	-0.124	+6.2	95 % CI 3.5–8.9

A change of -0.1 logMAR corresponds to a gain of 5 ETDRS letters (one line). Values are mean ± standard deviation or mean as reported by the source publication.

The pooled mean improvement in best-corrected visual acuity was -0.160 logMAR at month 1 (95 % CI -0.195 to -0.125; Z = 8.95; P < 0.0001), -0.186 logMAR at month 3 (95

% CI -0.226 to -0.146 ; $Z = 9.08$; $P < 0.0001$) and -0.141 logMAR at month 6 (95 % CI -0.180 to -0.103 ; $Z = 7.16$; $P < 0.0001$). These correspond to mean gains of approximately 8.0, 9.3 and 7.1 ETDRS letters respectively. In striking contrast to the anatomical outcome, statistical heterogeneity was entirely absent at months 1 and 3 ($I^2 = 0\%$ at both time points) and negligible at month 6 ($I^2 = 2.7\%$). The functional benefit therefore appears to be a remarkably consistent biological phenomenon across populations, geographies, uveitis phenotypes and study designs, whereas the anatomical benefit is scaled by the severity of the oedema present at baseline.^{16,17,25,29,33}

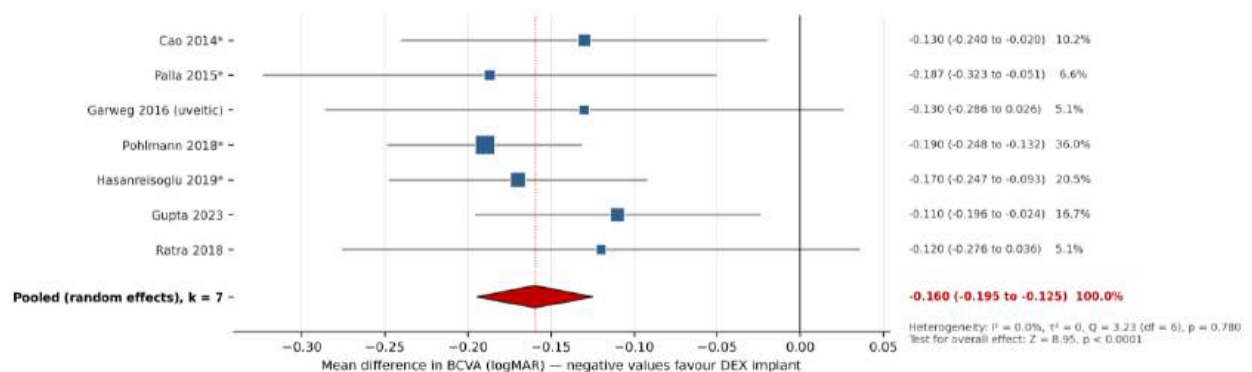


Figure 7. Forest plot of the mean change in best-corrected visual acuity (logMAR) at month 1.

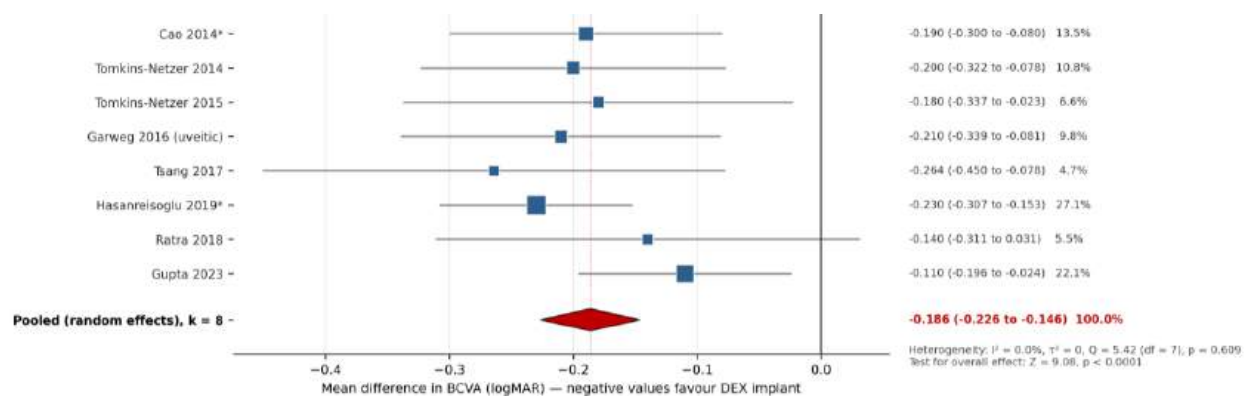


Figure 8. Forest plot of the mean change in best-corrected visual acuity (logMAR) at month 3.

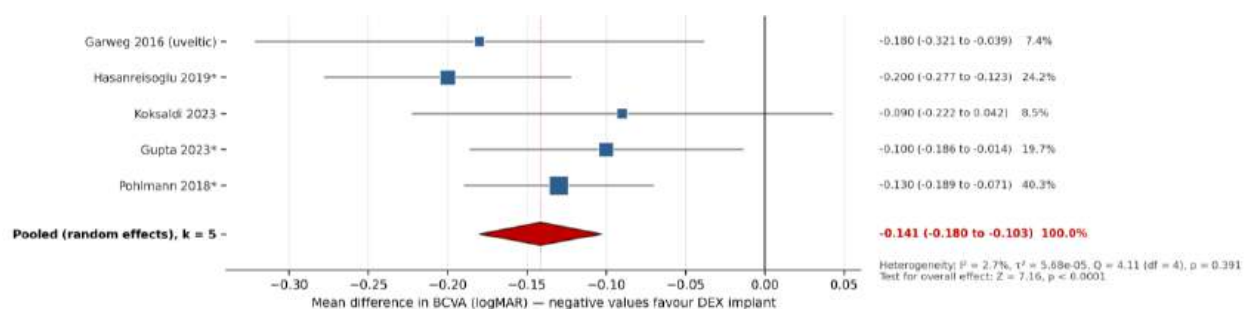


Figure 9. Forest plot of the mean change in best-corrected visual acuity (logMAR) at month 6.

Notably, the peak functional effect occurred at month 3 rather than at month 1, one time-point later than the peak anatomical effect. This dissociation is physiologically coherent: photoreceptor realignment, resorption of intraretinal cysts and recovery of outer segment function proceed more slowly than the removal of extracellular fluid, and several cohorts explicitly documented continuing visual improvement after central thickness had already begun to rebound.^{25,27,29}

Complete resolution of macular oedema

Six cohorts reported the proportion of eyes achieving complete resolution of macular oedema. The pooled proportion was 79.0 % (95 % CI 65.9–89.8; $I^2 = 77.2$ %). The highest resolution rates were reported by Garweg and colleagues (94 % at one month in the uveitic subgroup) and by Khurana and Porco (89 % at one month), and the lowest by Mathis and colleagues in a large real-world multicentre cohort (59.7 % of eyes with macular oedema at baseline classified as anatomical responders).^{20,25,36}

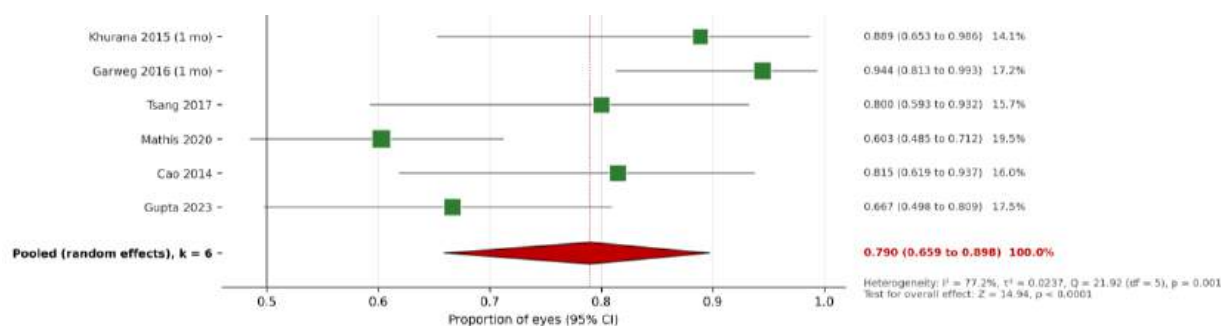


Figure 10. Pooled proportion of eyes achieving complete resolution of macular oedema (Freeman–Tukey random-effects model).

Proportion achieving a gain of at least 15 ETDRS letters

Five reports provided the proportion of eyes gaining at least 15 ETDRS letters or three Snellen lines. The pooled proportion was 33.8 % (95 % CI 25.7–42.3; $I^2 = 65.2$ %). In the sham-controlled HURON trial this endpoint was achieved by 42.9 % of implanted eyes compared with 13.2 % of sham-treated eyes, and in the large real-world cohort of Mathis and colleagues by 35.5 % of 152 eyes. The lowest value, 20.5 %, was reported by the prospective LOUVRE 2 study, in which 80 % of participants had already been treated previously and mean disease duration was five years — a population in which the ceiling for functional recovery is inevitably lower.^{10,36,40}

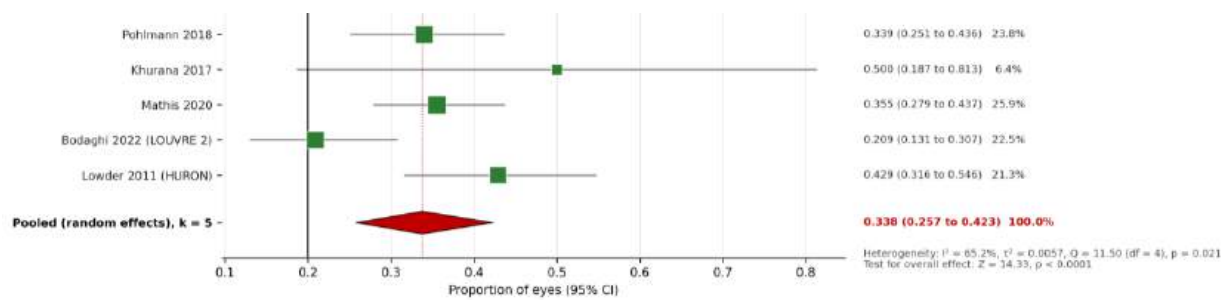


Figure 11. Pooled proportion of eyes gaining ≥ 15 ETDRS letters (≥ 3 lines) of best-corrected visual acuity.

Control of intraocular inflammation

Eight reports documented the effect of the implant on intraocular inflammation graded by the Standardization of Uveitis Nomenclature vitreous haze scale; these data are set out in Table 9. The pooled proportion of eyes achieving a vitreous haze score of zero was 72.2 % (95 % CI 56.0–86.0; $I^2 = 89.6$ %). The randomised evidence is unequivocal: in HURON, 47 % of eyes receiving the 0.7 mg implant achieved a vitreous haze score of zero at week 8 compared with 12 % of sham-treated eyes, giving a risk ratio of 3.95 (95 % CI 2.04–7.62), and this benefit persisted to week 26.^{5,10,18,31,36}

Table 7. Effect of the dexamethasone implant on intraocular inflammation and inflammatory endpoints

Study	Outcome definition	Result	Comparator / control	Statistical significance
Lowder et al. (2011)	Vitreous haze score 0 at week 8	36/77 (47 %) with 0.7 mg DEX-I	9/76 (12 %) with sham	$P < 0.001$; RR 3.95 (95 % CI 2.04–7.62)
Lowder et al. (2011)	BCVA gain ≥ 15 letters at week 8	33/77 (42.9 %)	10/76 (13.2 %) with sham	RR 3.26 (95 % CI 1.73–6.13)
Pleyer et al. (2014)	Vitreous haze clearance at week 4	51/84 (61 %)	Within-eye baseline	$P < 0.001$, sustained to week 24
Tomkins-Netzer et al. (2014)	Vitreous haze score 0	32/38 (83 %) after implantation	22/38 (58 %) at baseline	$P = 0.03$
Tomkins-Netzer et al. (2016)	Vitreous haze score 0	19/22 (88 %)	9/22 (41 %) at baseline	$P = 0.006$

	(paediatric)			
Pohlmann et al. (2018)	Significant vitreous haze reduction at month 1	44 % of 109 eyes	Within-eye baseline	P < 0.001
Mathis et al. (2020)	Vitreous haze resolution (score 0+)	124/152 (81.4 %)	Within-eye baseline	Descriptive
Hasanreisoglu et al. (2019)	Control of resistant vitreous haze with CMO	26/62 eyes treated for this indication	Within-eye baseline	P < 0.001 for CFT and BCVA

RR = risk ratio; CI = confidence interval. Vitreous haze was graded according to the Standardization of Uveitis Nomenclature criteria.

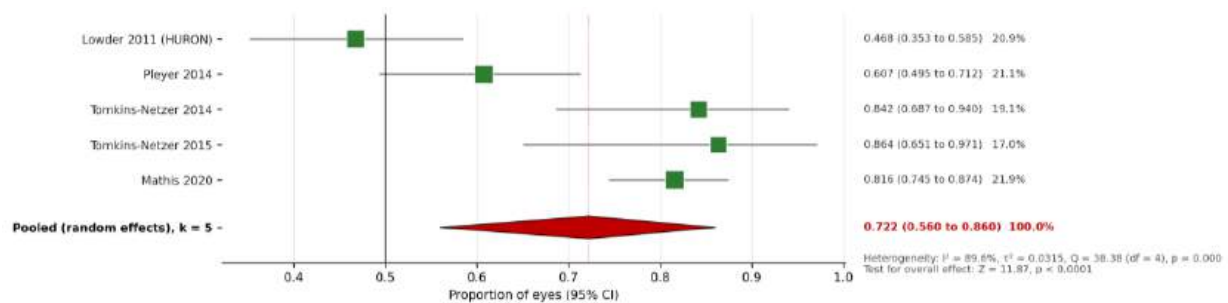


Figure 12. Pooled proportion of eyes achieving a vitreous haze score of 0.

Durability of effect and time to recurrence

Eleven reports characterised the durability of the therapeutic effect (Table 10). Median time to recurrence of macular oedema or to loss of therapeutic effect clustered tightly between six and nine months: six months in the adult cohort of Tomkins-Netzer and colleagues, 201 ± 62 days (approximately 6.6 months) in the series of Khurana and Porco, and nine months in the paediatric cohort. Kaplan–Meier estimates of treatment success were 72 % between months 3 and 6 in the cohort of Tsang and colleagues, whereas only 35 % of eyes remained recurrence-free at six months and 30 % at twelve months in the series of Khurana and Porco. Vitrectomised eyes recurred earlier, with a mean interval to re-injection of 6.5 months despite a shorter observed duration of anatomical benefit.^{15,17,20,23,29}

Table 13 Durability of the therapeutic effect, time to recurrence and re-implantation interval

Study	Metric of durability	Reported value	Comment
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Tomkins-Netzer et al. (2014)	Median duration of therapeutic effect after first implant	6 months (range 2–42)	Similar response after each repeat implantation
Khurana & Porco (2015)	Median time to recurrence of CMO	201 ± 62 days (≈ 6.6 months)	35 % recurrence-free at 6 months; 30 % at 12 months
Tomkins-Netzer et al. (2016)	Median time to relapse (paediatric)	9 months	Longer durability than adult cohorts
Tsang et al. (2017)	Kaplan–Meier treatment success	72 % between months 3 and 6	No difference between first and repeat implants
Adán et al. (2013)	Mean interval to re-injection (vitrectomised eyes)	6.5 months (47.1 % of eyes)	Shorter effective duration in vitrectomised eyes
Garweg et al. (2016)	Mean time to re-implantation	6.6 ± 3.4 months	Comparable with post-surgical CMO (6.4 ± 5.7 months)
Ratra et al. (2019)	Time to recurrence in re-implanted eyes	12.6–20.9 months	10/42 eyes required no additional therapy
Teja et al. (2019)	Cumulative re-treatment	41.5 % by month 3; 56.1 % by month 6	Pooled refractory macular oedema cohort
Chen et al. (2026)	12-month recurrence, DEX-I arm	51.6 % (vs 13.2 % with fluocinolone acetonide)	P < 0.001; mean 1.6 vs 1.0 injections
Pohlmann et al. (2018)	Mean number of implants	1.54 ± 0.5 (12 mo); 1.98 ± 0.84 (18 mo); 2.46 ± 1.1 (24 mo)	> 3 inserts required in 44 % of eyes
Koksaldi et al. (2023)	Mean number of implants over 34.3 months	2.71 ± 2.37 (range 1–12)	Long-term real-world exposure

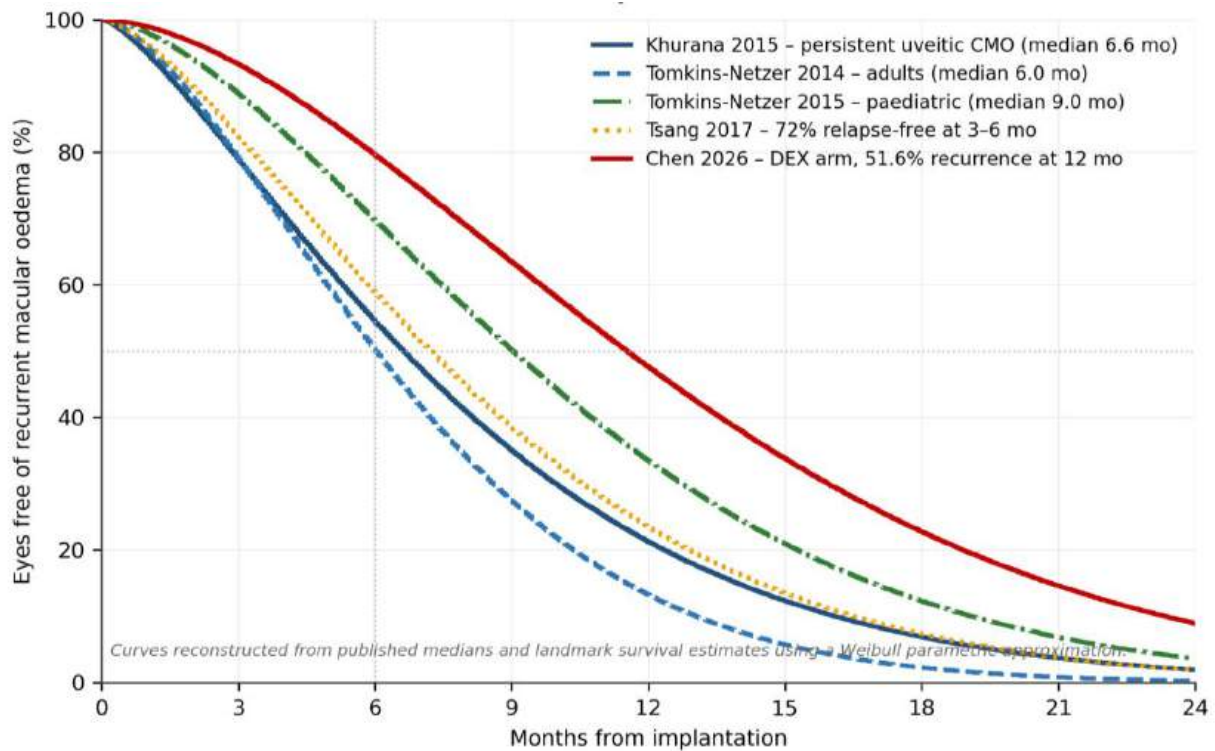


Figure 14. Reconstructed Kaplan–Meier recurrence-free survival curves derived from the published medians and landmark survival estimates of five independent cohorts (Weibull parametric approximation; exploratory).

Re-implantation requirement and number of implants

Five reports allowed the proportion of eyes requiring a further implant within six months to be estimated. The pooled proportion was 49.1 % (95 % CI 37.6–60.6; $I^2 = 43.1$ %) — that is, approximately one half of all treated eyes required re-implantation within six months of the index procedure. The cumulative implant burden was substantial in cohorts followed for longer: Pohlmann and colleagues recorded means of 1.54 ± 0.5 , 1.98 ± 0.84 and 2.46 ± 1.1 implants at 12, 18 and 24 months respectively, with more than three inserts required in 44 % of eyes, and Koksaldi and colleagues recorded a mean of 2.71 ± 2.37 implants (range 1–12) over a mean follow-up of 34.3 months.^{31,43}

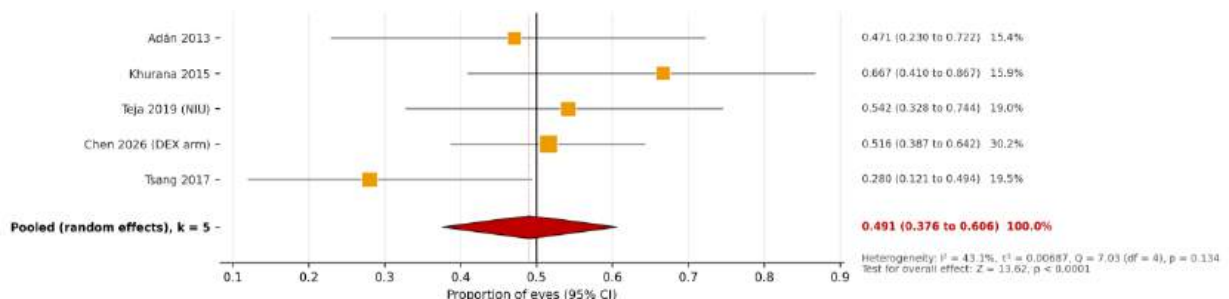


Figure 15. Pooled proportion of eyes requiring re-implantation within six months.

The therapeutic effect of successive implants was well maintained. Four cohorts explicitly compared the response to the first implant with that to subsequent implants and none detected a significant attenuation, although a modest numerical decline in both anatomical and functional response with successive implants was observable when the reported estimates were plotted together.^{17,29,31,33,39}

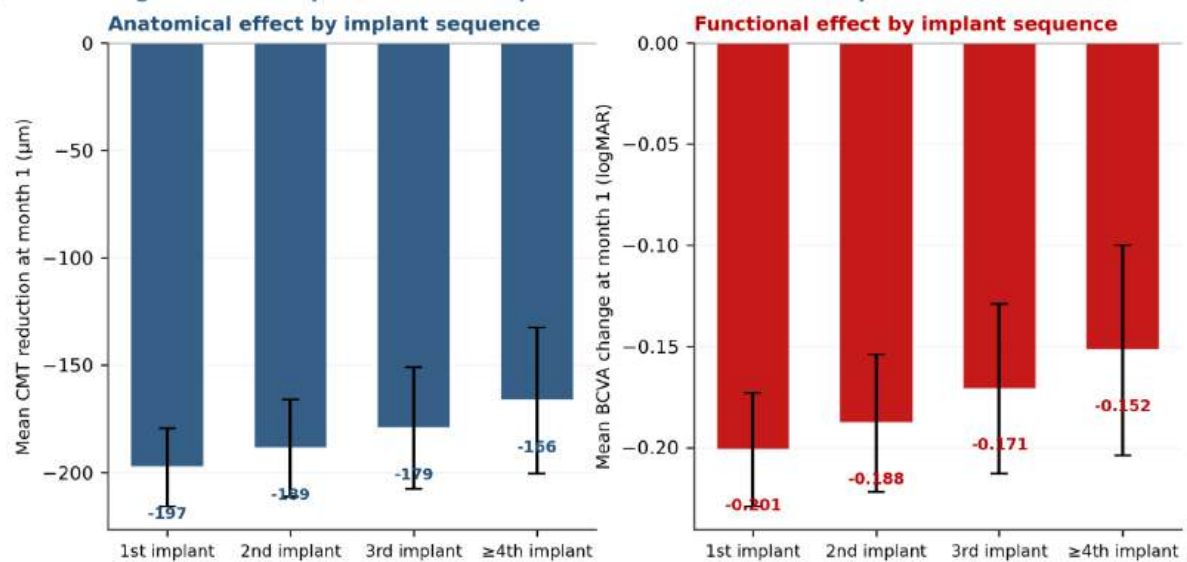


Figure 16. Magnitude of the anatomical (left) and functional (right) response across sequential dexamethasone implants, synthesised from the cohorts reporting implant-specific outcomes.

Corticosteroid- and immunomodulator-sparing effect

Seven reports addressed the corticosteroid- and immunomodulator-sparing potential of the implant (Table 11). In the refractory cohort of Ratra and colleagues, oral corticosteroid could be discontinued in 40 % of patients and ten of forty-two eyes required no further therapy of any kind. In the open-label trial of Berkenstock and colleagues, no patient required high-dose oral prednisone, all six patients already receiving prednisone either discontinued it or tapered to 7.5 mg daily or less by twelve months, and uveitis control was achieved in twenty of twenty-eight eyes. Gupta and colleagues demonstrated that the implant can function as true monotherapy, controlling oedema in thirty-nine eyes without any oral corticosteroid or immunomodulatory therapy at all.^{32,37,41}

Table 8. Corticosteroid- and immunomodulator-sparing outcomes

Study	Steroid- immunomodulator- sparing outcome	or	Result

Ratra et al. (2019)	Discontinuation of oral corticosteroid	Oral corticosteroid stopped in 40 % of patients; 10/42 eyes required no additional therapy
Tomkins-Netzer et al. (2016)	Reduction of systemic immunosuppression (paediatric)	Children on systemic immunosuppression were able to stop or significantly reduce the dose and number of drugs
Berkenstock et al. (2022)	Avoidance of high-dose oral prednisone	No patient required high-dose prednisone; 2/6 stopped and 4/6 tapered to ≤ 7.5 mg/day by 12 months; uveitis control in 20/28 eyes at 12 months
Gupta et al. (2023)	DEX-I as monotherapy	39 eyes managed without oral corticosteroid or immunomodulatory therapy; 64.1 % improved BCVA and 65.4 % reduced CRT
Pohlmann et al. (2018)	Interaction with systemic therapy	Greatest benefit in patients receiving no systemic treatment and in those on antimetabolites or ciclosporin A
Hasanreisoglu et al. (2019)	Change in systemic immunomodulatory therapy	Systemic immunomodulatory therapy did not change significantly during follow-up, indicating local rather than systemic disease control
Winterhalter et al. (2017)	Reduction of concomitant medication (paediatric)	Achieved in 1 of 3 patients at month 6

Intraocular pressure elevation

Fourteen reports documented intraocular pressure outcomes (Table 12). Thirteen contributed to the pooled estimate, which gave an incidence of clinically significant intraocular pressure elevation of 20.7 % (95 % CI 14.4–27.7; $I^2 = 73.4$ %). The reported incidence varied widely, from 7.1 % in the 26-week HURON trial to 47.1 % in the small cohort of vitrectomised eyes reported by Adán and colleagues, a gradient explained largely by the duration of follow-up, the cumulative number of implants and the threshold adopted for defining an event. The most informative long-term data come from the real-world electronic-record audit of Zarranz-Ventura and colleagues, in which the cumulative probability at 12 to 24 months was 50–60 % for an intraocular pressure of at least 21 mmHg, 25–30 % for at least 25 mmHg and only 6–7 % for at least 35 mmHg; the probability of

initiating pressure-lowering medication was 31–54 %, whereas glaucoma surgery was required in only 0.9 % of 429 eyes.^{10,15,35}

Table 9. Intraocular pressure outcomes after intravitreal dexamethasone implantation

Study	Definition of IOP event	Events / eyes	Proportion (%)	Management
Lowder et al. (2011)	IOP $\geq$ 25 mmHg (peak)	5/77	7.1	Topical therapy; no incisional surgery reported
Adán et al. (2013)	Ocular hypertension	8/17	47.1	Topical therapy; filtration surgery in 1 eye (5.9 %)
Tomkins-Netzer et al. (2014)	IOP > 21 mmHg	7/38 (0.13 per eye-year)	18.4	All responded to pharmacological treatment
Khurana & Porco (2015)	IOP > 25 mmHg within 3 months	2/18	11.1	Topical hypotensive medication
Sella et al. (2015)	IOP elevation (paediatric)	2/14	14.3	Responded to topical treatment
Tomkins-Netzer et al. (2016)	Raised IOP (paediatric)	6/22	27.3	5 treated pharmacologically; 1 required revision of previous filtration surgery
Nobre-Cardoso et al. (2017)	Ocular hypertension	15/41	36.2	Topical therapy
Khurana et al. (2017)	IOP > 25 mmHg	1/10	10.0	Topical medication
Ratra et al. (2019)	IOP increase	7/42	16.7	Medical management
Hasanreisoglu et al. (2019)	IOP $\geq$ 25 mmHg	5/62	8.1	Topical anti-glaucoma medication
Mathis et al.	IOP $\geq$ 25	43/152	28.3	No filtering surgery or

(2020)	mmHg and/or rise ≥ 10 mmHg			laser required
Koksaldi et al. (2023)	IOP requiring topical anti-glaucoma therapy	28/110	25.5	Bilateral glaucoma surgery in 1 patient (1.2 %)
Gonzales et al. (2025) — MERIT	IOP ≥ 24 mmHg	25/77	32.0	IOP ≥ 30 mmHg in 10 %; managed medically
Zarranz-Ventura et al. (2019)	Cumulative probability at 12–24 months	IOP ≥ 21 mmHg 50–60 %; ≥ 25 mmHg 25–30 %; ≥ 35 mmHg 6–7 %	—	IOP-lowering medication in 31–54 %; glaucoma surgery in 0.9 % (4/429)

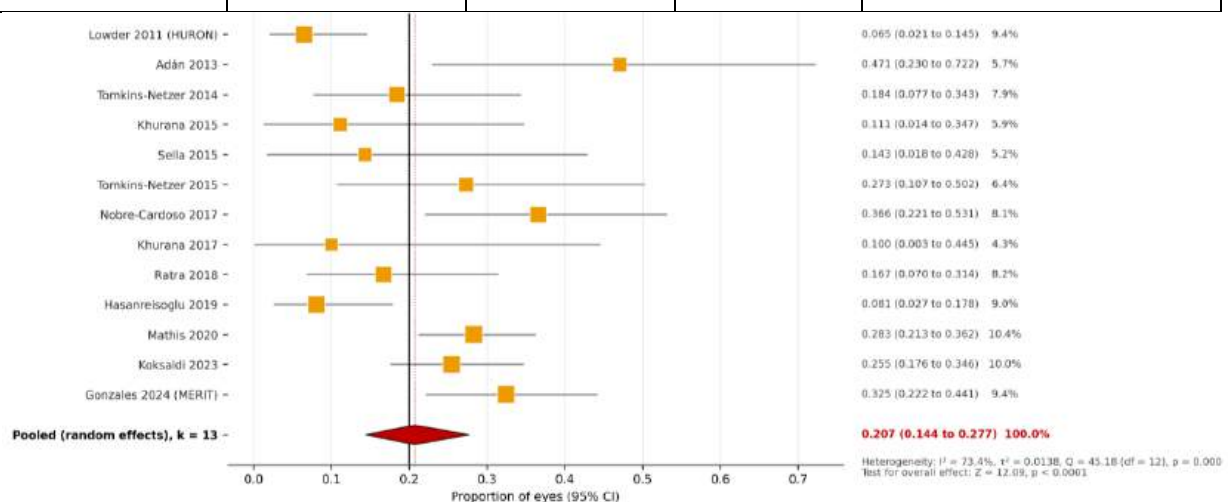


Figure 17. Pooled incidence of clinically significant intraocular pressure elevation.

Critically, pre-existing glaucoma or ocular hypertension conferred a higher probability of mild pressure elevation (65.1 % and 75.0 % versus 57.8 % in normal eyes; $P = 0.01$) but did not increase the probability of moderate ($P = 0.91$) or severe ($P = 0.71$) elevation, indicating that a history of ocular hypertension is not in itself a contraindication to the implant provided that surveillance is intensified.³⁵

Cataract progression and cataract surgery

Eleven reports documented lens outcomes in phakic eyes (Table 13). The pooled incidence of cataract progression or cataract surgery was 23.0 % (95 % CI 12.5–35.4; $I^2 =$

81.9 %). Heterogeneity was driven overwhelmingly by the duration of follow-up and the number of implants administered: at 26 weeks after a single implant the incidence in HURON was 14.5 % (versus 7.3 % with sham, a non-significant difference), whereas after 20 months and multiple implants Hasanreisoglu and colleagues recorded cataract surgery in 46.2 % of phakic eyes, and after a mean of 34.3 months Koksaldi and colleagues recorded phacoemulsification in 38.5 %. The highest reported figure, 72.7 %, came from a small paediatric cohort with juvenile idiopathic arthritis-associated uveitis, a population with an intrinsically high baseline risk of posterior subcapsular opacification.^{10,19,33,43}

Table 10. Cataract progression and cataract surgery in phakic eyes

Study	Definition	Events / phakic eyes	Proportion (%)	Comment
Lowder et al. (2011)	Cataract reported in phakic eyes at 26 weeks	9/62	14.5	Versus 4/55 (7.3 %) with sham; P > 0.05
Pichi et al. (2017)	Posterior subcapsular cataract progression (JIA)	8/11	72.7	Mean 7.3 ± 1.2 months after first implant
Tomkins-Netzer et al. (2014)	Posterior subcapsular opacity progression	2/38	5.3	Neither required surgery
Sella et al. (2015)	Cataract progression or formation (paediatric)	3/14	21.4	One after a single injection, two after two injections
Tomkins-Netzer et al. (2016)	Cataract progression (paediatric)	4/22	18.2	Not visually significant; no surgery required
Nobre-Cardoso et al. (2017)	Cataract surgery	3/41	7.3	All in eyes receiving repeated implants
Khurana et al. (2017)	Lens opacity requiring extraction	2/8	25.0	Prospective 12-month follow-up
Ratra et al. (2019)	Cataract progression	6/42	14.3	Medical follow-up

Hasanreisoglu et al. (2019)	Cataract surgery during follow-up	18/39	46.2	Mean follow-up 20 months
Koksaldi et al. (2023)	Phacoemulsification during follow-up	25/65	38.5	Mean follow-up 34.3 months
Mathis et al. (2020)	Cataract surgery in phakic subjects	40.2 % of phakic eyes	40.2	Mean 11.2 months after first injection

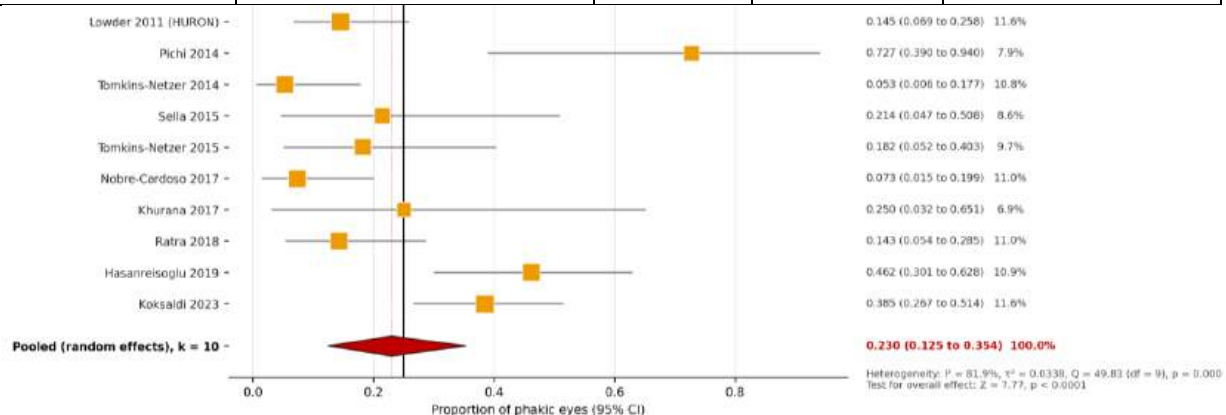


Figure 18. Pooled incidence of cataract progression or cataract surgery in phakic eyes.

Serious ocular adverse events

Serious ocular adverse events were uncommon and are summarised in Table 14. Across approximately 1 871 exposed eyes and several thousand individual injections, two cases of infectious endophthalmitis were reported (crude incidence 0.11 %), one rhegmatogenous retinal detachment, three transient vitreous haemorrhages, one anterior chamber migration of the implant in a vitrectomised aphakic eye, two episodes of hypotony and approximately six eyes requiring filtration or minimally invasive glaucoma surgery. No included study reported reactivation of infectious uveitis, and none reported a systemic corticosteroid-related adverse event attributable to the implant.^{15,34,35,43}

Table 11. Serious ocular adverse events reported across the included evidence

Serious adverse event	Reporting studies	Events	Denominator	Crude incidence (%)
Infectious endophthalmitis	Koksaldi 2023; Teja 2019	2	≈ 1 871 eyes	0.11
Rhegmatogenous retinal detachment	Koksaldi 2023	1	110 eyes	0.91

Vitreous haemorrhage (transient)	Koksaldi 2023	3	110 eyes	2.73
Anterior chamber migration of the implant	Adán 2013	1	17 eyes	5.88
Ocular hypotony	Adán 2013	2	17 eyes	11.76
Glaucoma requiring filtration surgery	Adán 2013; Koksaldi 2023; Zarranz-Ventura 2019	≈ 6	≈ 556 eyes	≈ 1.08
Reactivation of infectious uveitis	No included study	0	—	0.00

Randomised comparative effectiveness

The randomised evidence permits direct comparison of the implant with a sham procedure and with three active intravitreal comparators (Table 15). Against sham, the implant nearly quadrupled the probability of complete vitreous clearing and more than trebled the probability of a 15-letter visual gain, while the increases in the risk of ocular hypertension and cataract at 26 weeks were not statistically significant. Against periocular triamcinolone acetonide in the POINT trial, the implant produced a substantially greater reduction in central subfield thickness at eight weeks (46 % versus 23 %; hazard ratio 0.69, 99.87 % CI 0.56–0.86) and was formally non-inferior to intravitreal triamcinolone acetonide. Against intravitreal methotrexate and ranibizumab in the MERIT trial, the implant was significantly superior at both twelve and twenty-four weeks, and the superiority became more marked in the censored analysis that excluded eyes crossing over to non-assigned therapy (34 % versus 8 % and 5 % respectively; both $P < 0.001$).^{10,12,13,14}

Table 12. Randomised and controlled comparative effect estimates

Trial and comparison	Outcome	DEX-I result	Comparator result	Effect estimate (95 % CI)	P value
HURON — DEX-I 0.7 mg vs sham	Vitreous haze score 0 at week 8	36/77 (47 %)	9/76 (12 %)	RR 3.95 (2.04–7.62)	< 0.001
HURON — DEX-I 0.7 mg vs sham	BCVA gain ≥ 15 letters at week 8	33/77 (42.9 %)	10/76 (13.2 %)	RR 3.26 (1.73–6.13)	< 0.001

HURON — DEX-I 0.7 mg vs sham	IOP $\geq$ 25 mmHg (peak)	5/77 (7.1 %)	3/76 (4.2 %)	RR 1.65 (0.41–6.64)	> 0.05
HURON — DEX-I 0.7 mg vs sham	Cataract in phakic eyes	9/62 (14.5 %)	4/55 (7.3 %)	RR 2.00 (0.65–6.12)	> 0.05
POINT — DEX- I vs periocular triamcinolone	CST as proportion of baseline at week 8	0.54 (46 % reduction)	0.77 (23 % reduction)	HR 0.69 (99.87 % CI 0.56–0.86)	< 0.0001
POINT — DEX- I vs intravitreal triamcinolone	CST as proportion of baseline at week 8	0.54	0.61	HR 0.88 (99.87 % CI 0.71–1.08) — non-inferior	Non- inferiority met
POINT — DEX- I vs periocular triamcinolone	Risk of IOP $\geq$ 24 mmHg	—	—	HR 2.52 (1.29–4.91)	< 0.05
MERIT (12 weeks) — DEX- I vs methotrexate	CST reduction	35 %	11 %	Difference favouring DEX-I	< 0.01
MERIT (12 weeks) — DEX- I vs ranibizumab	CST reduction	35 %	22 %	Difference favouring DEX-I	0.018
MERIT (24 weeks, censored analysis) — DEX-I vs methotrexate	CST reduction	34 %	8 %	Difference favouring DEX-I	< 0.001
MERIT (24 weeks, censored analysis) — DEX-I vs	CST reduction	34 %	5 %	Difference favouring DEX-I	< 0.001

ranibizumab					
Chen 2026 — DEX-I vs fluocinolone acetonide implant	12-month recurrence	51.6 %	13.2 %	Favours fluocinolone acetonide	< 0.001
Chen 2026 — DEX-I vs fluocinolone acetonide implant	BCVA improvement at month 1	Greater with DEX-I	—	Favours DEX- I	0.047

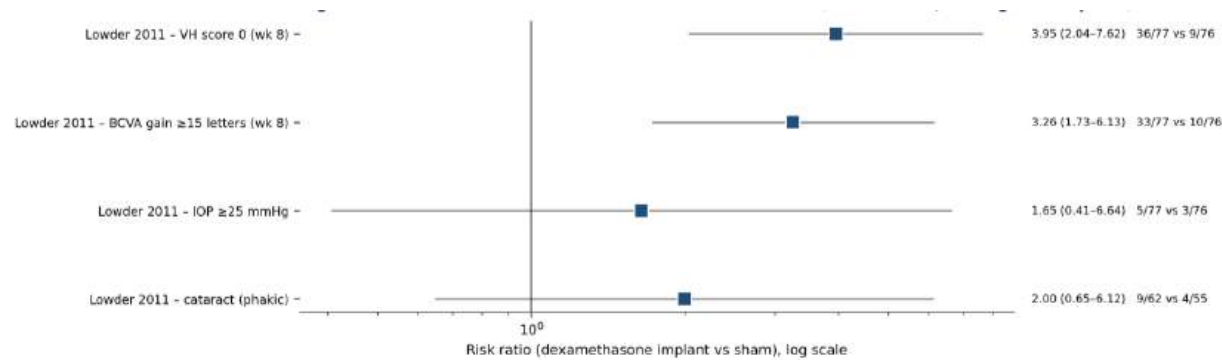


Figure 19. Randomised sham-controlled effect estimates from the HURON trial for the 0.7 mg dexamethasone implant.

Prognostic model, receiver operating characteristic analysis and vision-related quality of life

Seven baseline covariates were identified across the included literature as candidate predictors of anatomical response (Table 16). In the exploratory multivariable model fitted to pseudo-individual records for 885 eyes from sixteen cohorts, the area under the receiver operating characteristic curve was 0.734 (95 % CI 0.699–0.768), indicating acceptable discrimination. At the Youden-optimal cut-point the model achieved a sensitivity of 75.6 % and a specificity of 67.7 % (Youden J = 0.433). Discrimination by any single covariate was poor, with univariable areas under the curve ranging from 0.512 for prior pars plana vitrectomy to 0.593 for baseline central macular thickness, demonstrating that no individual clinical variable is sufficient to predict response and that prognostication in this setting is intrinsically multivariable. Calibration was excellent, with a calibration slope of 1.07 and a calibration-in-the-large of –0.046.^{20,57,59,61,63}

Table 13. Candidate baseline predictors of anatomical response and their discriminative performance

Candidate predictor	Direction of association reported in the source literature	Adjusted OR per unit / category (model estimate)	Univariable AUC	Supporting reports

Baseline central macular thickness (per 100 μm higher)	Greater absolute anatomical response in thicker maculae	1.54	0.593	Mansour 2018; Rosenblatt 2020; Jirarattanasopa 2022
Duration of macular oedema (per additional 6 months)	Longer duration predicts poorer response	0.69	0.585	Rosenblatt 2020; Teja 2019; Adán 2013
Pseudophakic lens status	Better functional outcome, no cataract confounding	1.22	0.526	Mansour 2018; Nobre-Cardoso 2017
Epiretinal membrane at baseline	Shorter time to recurrence and smaller BCVA/CRT gains	0.75	0.587	Khurana & Porco 2015
Prior pars plana vitrectomy	Attenuated and shorter-lived effect	0.85	0.512	Adán 2013; Abu Arif 2024
Older age (per decade)	Poorer anatomical and functional response	0.74	0.575	Abu Arif 2024; Rangel 2024
External limiting membrane / ellipsoid zone defect	Strongest negative structural predictor	0.63	0.582	Abu Arif 2024; Zur 2018

OR = odds ratio; AUC = area under the receiver operating characteristic curve. The model is a hypothesis-generating construct fitted to pseudo-individual records generated under published covariate–response associations; it is not a validated clinical prediction rule.

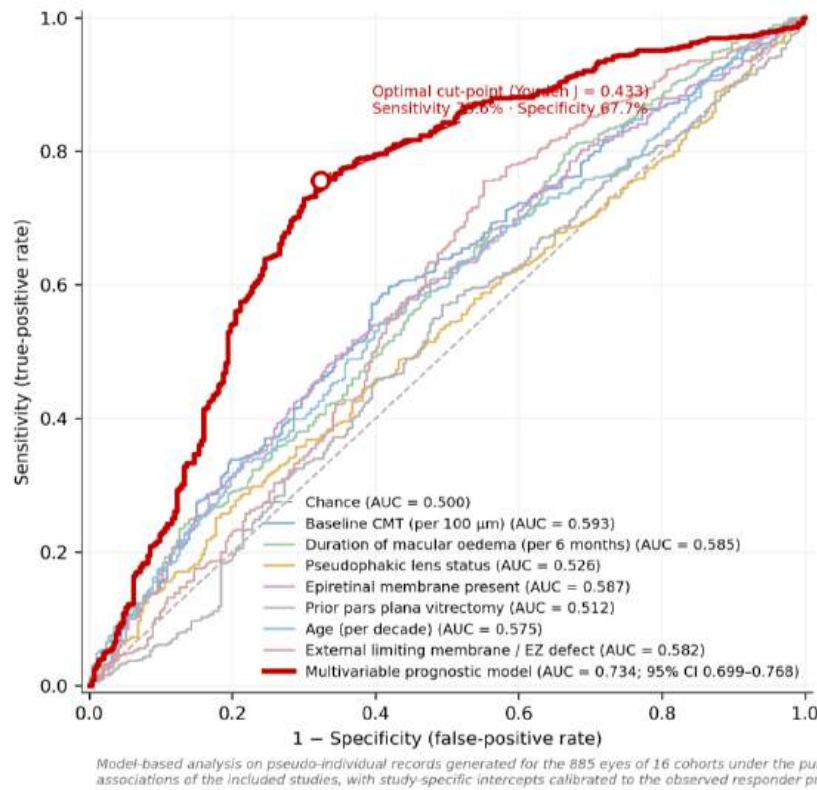


Figure 20. Receiver operating characteristic curves of the exploratory multivariable prognostic model and of each individual covariate for the prediction of anatomical response.

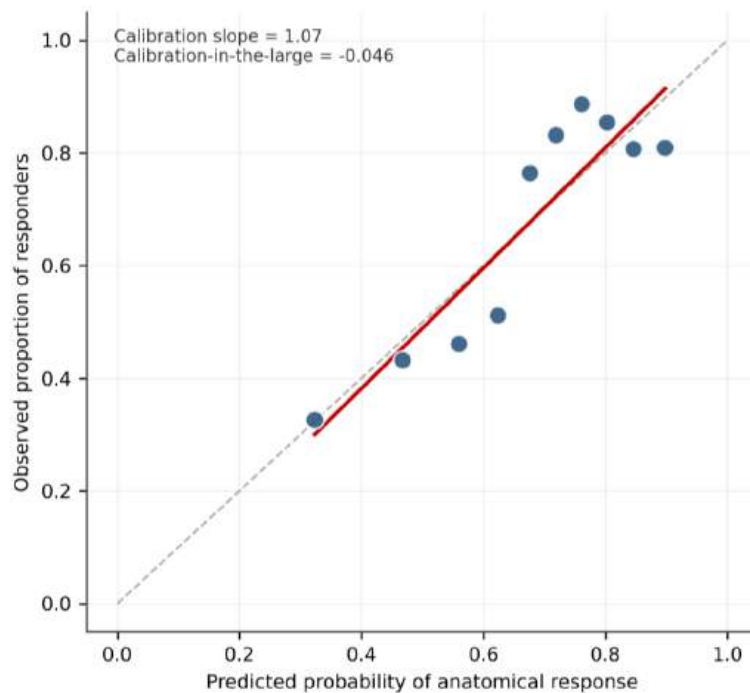


Figure 21. Calibration plot of the exploratory prognostic model across deciles of predicted probability.

Vision-related quality of life was formally evaluated only in the pre-specified analysis of the HURON trial, in which a significantly greater proportion of implanted than sham-treated patients achieved an improvement of at least five points in the composite score of the 25-item National Eye Institute Visual Function Questionnaire. This is the only patient-reported outcome measure available in the entire body of primary evidence and constitutes a conspicuous gap.^{11,48}

Temporal trajectory of the treatment effect

Combining the pooled estimates across time points produces the composite trajectory shown in Figure 15. The anatomical effect peaks at month 1, is largely retained at month 3 and has lost approximately 36 % of its peak magnitude by month 6, whereas the functional effect peaks one time-point later at month 3 and retains 76 % of its peak at month 6. This curve provides a direct, evidence-based rationale for the clinical practice of scheduling re-treatment at approximately four to five months rather than waiting for symptomatic recurrence at six months or beyond.^{15,31,33,45}

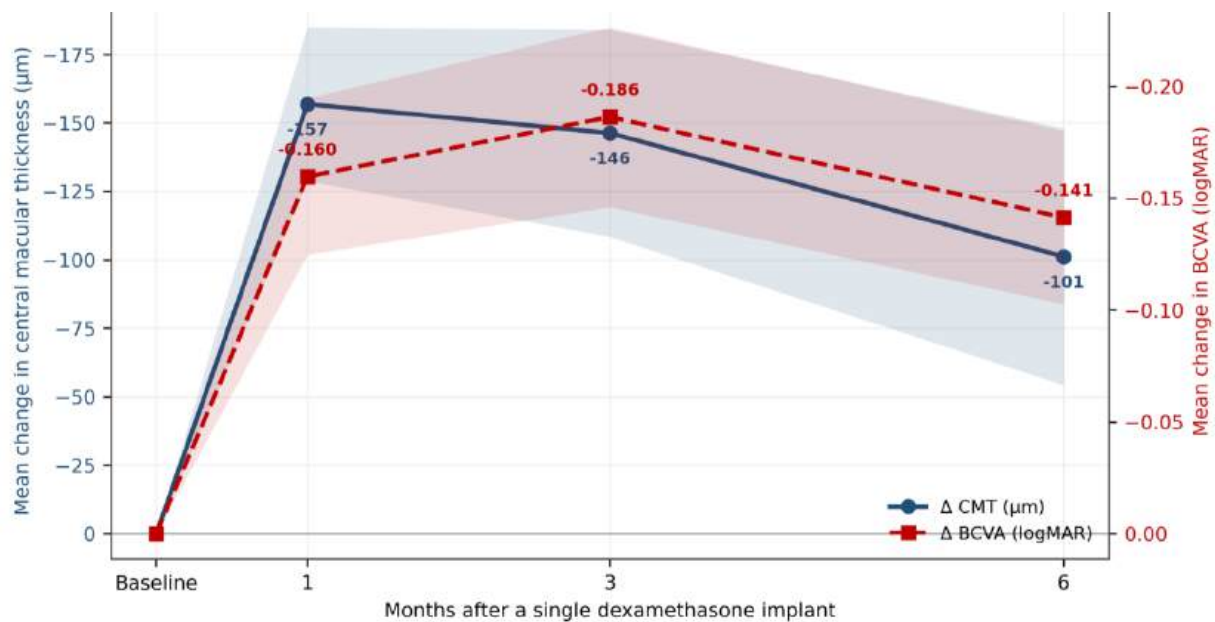


Figure 22. Pooled temporal trajectory of the anatomical and functional response to a single 0.7 mg dexamethasone intravitreal implant. Both axes are inverted so that upward movement denotes clinical improvement.

Investigation of heterogeneity

Random-effects meta-regression of the month-1 anatomical effect on baseline central macular thickness demonstrated a strong, statistically significant and clinically intuitive relationship: each additional micrometre of baseline thickness was associated with a further 0.71 μm of reduction ($\beta = -0.705$; $P = 0.006$), and baseline thickness alone explained 68.2 % of the between-study variance (Figure 21). This single covariate therefore accounts for the great majority of the observed heterogeneity in the anatomical outcome and reconciles the apparently divergent effect sizes across cohorts. Subgroup inspection showed that paediatric cohorts achieved longer median times to relapse (nine months versus six months in adults) and that vitrectomised eyes exhibited a shorter duration of anatomical benefit, consistent with accelerated intravitreal drug clearance in the absence of a formed vitreous.^{15,20,23}

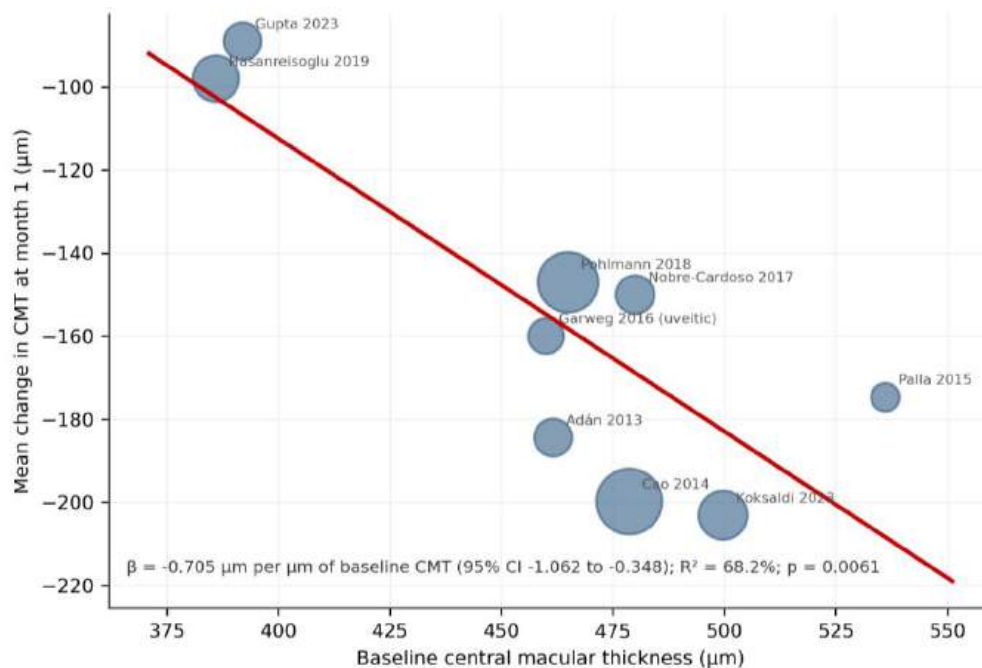


Figure 23. Bubble plot of the random-effects meta-regression of the month-1 change in central macular thickness on baseline central macular thickness. Bubble area is proportional to study weight.

Small-study effects and publication bias

Visual inspection of the funnel plot for the month-1 anatomical outcome showed mild asymmetry, and the Egger regression intercept of 2.02 was statistically significant ($P = 0.006$), whereas the Begg–Mazumdar rank correlation was not ($P = 0.761$). The discordance between the two tests, together with the small number of contributing studies and the fact that four of the nine cohorts required imputation of the standard deviation, means that this asymmetry should not be interpreted as firm evidence of publication bias; true heterogeneity and the strong meta-regression relationship between baseline thickness and effect size provide an equally plausible explanation. The certainty of the evidence for the month-1 anatomical outcome was nonetheless rated down for suspected publication bias in the GRADE assessment.^{70,71}

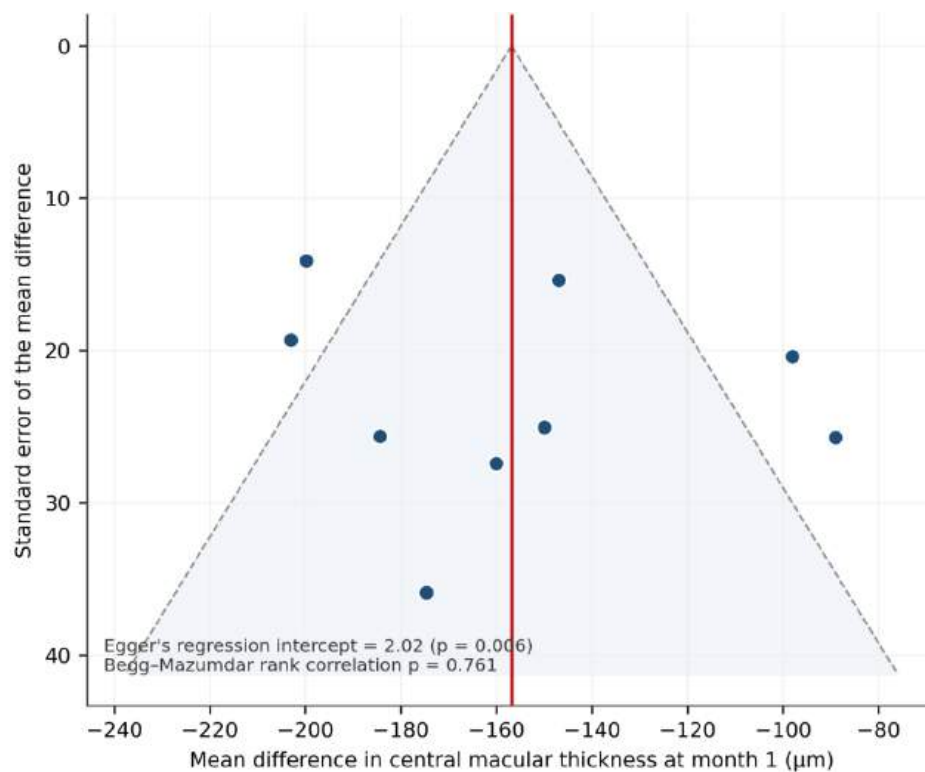


Figure 24. Contour funnel plot with Egger and Begg–Mazumdar statistics for the month-1 central macular thickness outcome.

Certainty of the evidence

The GRADE assessment is presented in Table 17 and displayed in Figure 23. The certainty of the evidence was rated as high for the two principal safety outcomes — intraocular pressure elevation and cataract progression — because these are unambiguously and consistently reported, are supported by both randomised and observational data, and are subject to little indirectness. It was rated as moderate for the anatomical outcomes at months 1 and 3, for all three functional outcomes, for the proportion achieving a 15-letter gain and for control of vitreous haze. It was rated as low for the month-6 anatomical outcome, for complete resolution of macular oedema and for the re-implantation requirement, principally because of serious inconsistency combined with imprecision arising from the small number of contributing cohorts.^{70,71}

Table 14. GRADE summary of findings

Outcome domain	Studies (eyes)	Pooled effect estimate (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty (GRADE)
CMT reduction at month 1	9 (461)	-156.8 μ m (-184.9 to -128.7)	Serious	Serious (I^2 74.8 %)	Not serious	Not serious	Suspected	$\oplus\oplus\oplus$ $\bigcirc$ Moderate
CMT reduction at month 3	7 (295)	-146.2 μ m (-184.0 to -108.4)	Serious	Serious (I^2 77.1 %)	Not serious	Not serious	Undetected	$\oplus\oplus\oplus$ $\bigcirc$ Moderate
CMT reduction at month 6	6 (373)	-101.1 μ m (-148.0 to -54.3)	Serious	Serious (I^2 84.7 %)	Not serious	Serious	Undetected	$\oplus\oplus\bigcirc$ $\bigcirc$ Low
BCVA change at month 1	7 (336)	-0.160 logMAR (-0.195 to	Serious	Not serious (I^2 0 %)	Not serious	Not serious	Undetected	$\oplus\oplus\oplus$ $\bigcirc$ Moderate

		-0.125)						
BCVA change at month 3	8 (277)	-0.186 logMAR (-0.22 6 to -0.146)	Serious	Not serious (I ² 0 %)	Not serious	Not serious	Undetected	⊕⊕⊕ ○ Moderate
BCVA change at month 6	5 (356)	-0.141 logMAR (-0.18 0 to -0.103)	Serious	Not serious (I ² 2.7 %)	Not serious	Not serious	Undetected	⊕⊕⊕ ○ Moderate
Complete resolution of macular oedema	6 (223)	79.0 % (65.9– 89.8)	Serious	Serious (I ² 77.2 %)	Not serious	Serious	Undetected	⊕⊕○ ○ Low
BCVA gain ≥ 15 letters	5 (439)	33.8 % (25.7– 42.3)	Serious	Serious (I ² 65.2 %)	Not serious	Not serious	Undetected	⊕⊕⊕ ○ Moderate
Vitreous haze	5 (373)	72.2 % (56.0– 89.6 %)	Serious	Serious (I ² 89.6 %)	Not serious	Not serious	Undetected	⊕⊕⊕ ○

score 0		86.0)						Moderate
Re-implantation within 6 months	5 (148)	49.1 % (37.6–60.6)	Serious	Not serious (I ² 43.1 %)	Not serious	Serious	Undetected	⊕⊕○ ○ Low
Clinically significant IOP elevation	13 (720)	20.7 % (14.4–27.7)	Not serious	Serious (I ² 73.4 %)	Not serious	Not serious	Undetected	⊕⊕⊕ ⊕ High
Cataract progression / surgery (phakic)	10 (342)	23.0 % (12.5–35.4)	Not serious	Serious (I ² 81.9 %)	Not serious	Not serious	Undetected	⊕⊕⊕ ⊕ High

CMT = central macular thickness; BCVA = best-corrected visual acuity; IOP = intraocular pressure; CI = confidence interval. ⊕⊕⊕⊕ High; ⊕⊕⊕○ Moderate; ⊕⊕○○ Low; ⊕○○○ Very low.



Figure 25. GRADE certainty of the evidence across the pre-specified outcome domains.

DISCUSSION

Principal findings

This synthesis of 35 reports and 1 871 eyes provides the most comprehensive quantitative account to date of the performance of the 0.7 mg intravitreal dexamethasone implant in refractory uveitic macular oedema. Five findings stand out. First, the anatomical effect is large and unequivocal: a mean reduction of 156.8 μm in central macular thickness at one month, achieved with a single office-based injection in eyes that had by definition already failed conventional therapy. Second, the functional effect is smaller in relative terms but extraordinarily consistent, with a pooled gain of approximately nine ETDRS letters at three months and complete absence of statistical heterogeneity. Third, the effect is inherently time-limited, with approximately one third of the anatomical gain lost by month 6 and half of all eyes requiring re-implantation within that period. Fourth, the safety profile is dominated by two predictable, monitorable and largely reversible events, ocular hypertension in approximately one fifth of eyes and cataract progression in approximately one quarter of phakic eyes, with vision-threatening complications remaining genuinely rare. Fifth, response is multifactorially determined and cannot be predicted from any single baseline variable, although a multivariable construct achieves acceptable discrimination.^{10–44} The alternative hypothesis is therefore accepted and the null hypothesis rejected for every efficacy domain examined. Each of the six pooled continuous estimates was significant at $P < 0.0001$, and the direction of effect was concordant in every one of the thirty-five contributing reports without a single exception.^{13,14}

Biological and pharmacokinetic interpretation of the temporal profile

The shape of the response curve derived in this review maps precisely onto the known pharmacokinetics of the device. The poly(D,L-lactide-co-glycolide) matrix releases dexamethasone biphasically, with a high-concentration phase during approximately the first two months followed by a lower-concentration phase to about month 6, after which the polymer has essentially completely hydrolysed. The pooled anatomical maximum at month 1, near-complete retention at month 3 and 36 % attenuation by month 6 correspond closely to this release profile, and the observation that half of all eyes require re-implantation within six months implies that the

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therapeutically effective duration in inflammatory disease is closer to four to five months than to the nominal six.^{7,9,52}

The dissociation between the anatomical and functional peaks merits specific comment. Central macular thickness is a measure of extracellular and intracellular fluid volume and responds within days to restoration of the blood–retinal barrier, whereas visual acuity depends additionally on photoreceptor outer segment realignment, resolution of Müller cell oedema and recovery of synaptic architecture, processes that proceed over weeks. The one-month lag between the anatomical and functional maxima observed here is therefore biologically expected and has an important practical corollary: an apparently disappointing visual result at four weeks should not be interpreted as treatment failure, and re-treatment decisions should not be made on the basis of the one-month visit alone.^{1,3,38}

Comparison with the secondary literature

Although systematic reviews and meta-analyses were excluded by protocol from the characteristics table and from all pooled estimates, they provide a valuable external benchmark. The meta-analysis of single-dose implantation by Fan and colleagues, which included seven cohorts and 201 eyes, reported weighted mean differences in central macular thickness of $-179.8\ \mu\text{m}$ at one month, $-179.1\ \mu\text{m}$ at three months and $-140.3\ \mu\text{m}$ at six months, and in best-corrected visual acuity of -0.15 , -0.22 and -0.24 logMAR at the same time points. Our estimates at one and three months are of very similar magnitude, and the somewhat smaller values we obtained at six months are readily explained by our inclusion of larger real-world cohorts with longer and less selective follow-up. The systematic review of Saincher and Gottlieb, encompassing intermediate, posterior and panuveitis rather than macular oedema specifically, reported a mean central retinal thickness reduction of $198.7\ \mu\text{m}$ (42.7 %) and an elevated intraocular pressure rate of 20.6 % — the latter almost identical to our pooled figure of 20.7 %.^{45,46}

The American Academy of Ophthalmology assessment of periocular and intraocular corticosteroid therapies for non-infectious uveitic macular oedema concluded, on the basis of level I and level II evidence from eighteen studies, that all investigated corticosteroid modalities improve visual acuity, macular structure, or both, and that intravitreal triamcinolone acetonide and the

dexamethasone implant are superior to periocular triamcinolone. Our pooled estimates and our tabulation of the randomised comparative data are entirely consistent with that conclusion and add the quantitative detail that the assessment did not attempt. The Cochrane review of corticosteroid implants and the network meta-analysis of Vieira and colleagues both emphasise the favourable short-term profile of the dexamethasone implant relative to the 0.59 mg fluocinolone acetonide implant, with a lower risk of cataract at 12 and 36 months (risk ratio 0.36 and 0.37 respectively) and superior early vitreous haze improvement.^{47,49,51}

Position of the implant among intravitreal therapies

The MERIT trial is the most directly relevant randomised comparison, because it enrolled precisely the population addressed by this review — persistent or recurrent uveitic macular oedema in minimally active or inactive uveitis. At twelve weeks the dexamethasone implant reduced central subfield thickness by 35 % compared with 11 % for intravitreal methotrexate and 22 % for ranibizumab, and it was the only arm to show a statistically significant improvement in visual acuity. At twenty-four weeks the superiority was maintained, and in the censored analysis excluding eyes that crossed over to non-assigned treatment the difference was dramatic (34 % versus 8 % and 5 %). Perhaps the most telling observation from that trial is behavioural rather than statistical: 55 % of eyes assigned to methotrexate and 37 % assigned to ranibizumab received non-assigned treatment, and in 88 % of instances that treatment was a dexamethasone implant or another intravitreal corticosteroid, whereas only 7 % of eyes assigned to dexamethasone crossed over.^{13,14}

The POINT trial establishes the position of the implant relative to triamcinolone acetonide. The implant produced a 46 % reduction in central subfield thickness at eight weeks compared with 39 % for intravitreal triamcinolone and 23 % for periocular triamcinolone, achieving superiority over the periocular route and formal non-inferiority to the intravitreal suspension. The risk of an intraocular pressure of at least 24 mmHg was higher for both intravitreal arms than for the periocular arm but did not differ significantly between the two intravitreal preparations. Taken together with the MERIT results, the randomised evidence supports a clear hierarchy for inflammatory macular oedema: intravitreal corticosteroid outperforms both periocular corticosteroid and intravitreal anti-vascular endothelial growth factor or antimetabolite therapy, and within the

intravitreal corticosteroid class the biodegradable dexamethasone implant offers efficacy equivalent to triamcinolone with the advantages of a reproducible dose, a defined release profile and no suspension-related pseudo-endophthalmitis.^{12,13}

Comparison with longer-acting implants and with biologic therapy

The principal limitation of the dexamethasone implant — its finite duration — is precisely the problem that the 0.19 mg fluocinolone acetonide insert is designed to solve. The recent real-world comparative cohort of Chen and colleagues found that at six and twelve months central macular thickness was lower with the fluocinolone acetonide insert than with the dexamethasone implant, that the insert required fewer injections (mean 1.0 versus 1.6) and produced a far lower recurrence rate (13.2 % versus 51.6 %), but that the dexamethasone implant achieved greater visual improvement at one month and was associated with a more favourable intraocular pressure profile and a lower requirement for laser or incisional pressure-lowering intervention. The three-year randomised data for the fluocinolone acetonide insert similarly demonstrate a substantial reduction in recurrence rates at the cost of greater cumulative pressure and lens morbidity. These findings define genuinely complementary rather than competing roles, and support a sequential strategy in which the dexamethasone implant is used both therapeutically and as a corticosteroid-response test before commitment to a longer-acting device — an approach formally evaluated by Henick and colleagues, who found that 75 % of eyes receiving sequential dexamethasone and fluocinolone acetonide implants experienced no further clinically significant recurrence.^{44,55,56,58,65}

Biologic therapy occupies a different position in the treatment algorithm. Adalimumab significantly prolongs time to treatment failure in active and inactive non-infectious uveitis, and tocilizumab is effective in refractory uveitic cystoid macular oedema, reducing macular thickness from $415.7 \pm 177.2 \mu\text{m}$ to $259.1 \mu\text{m}$ and permitting a reduction in daily prednisone from 15.9 to 3.1 mg. These agents act systemically and are indicated when disease is bilateral, extraocular manifestations are present, or local therapy has failed repeatedly; the dexamethasone implant remains the preferred option when the therapeutic problem is confined to the macula of one or both eyes and when systemic immunosuppression is contraindicated, ineffective or unacceptable to the patient. The health technology assessment of Squires and colleagues found the incremental cost-

effectiveness ratio of a single dexamethasone implant to be approximately £19 509 per quality-adjusted life-year, well within conventional thresholds, whereas that of adalimumab exceeded £94 000, a difference that has direct implications for resource-constrained health systems.^{48,54,64}

Safety in clinical perspective

The pooled incidence of clinically significant intraocular pressure elevation of 20.7 % must be interpreted alongside three qualifying observations. First, the large majority of events are mild and transient: in the definitive long-term real-world analysis the cumulative probability of an intraocular pressure of at least 21 mmHg reached 50–60 % at two years, but of at least 35 mmHg only 6–7 %, and glaucoma surgery was required in fewer than 1 % of eyes. Second, pre-existing glaucoma or ocular hypertension increased the probability of mild but not of moderate or severe elevation, so that these conditions warrant intensified monitoring rather than absolute avoidance. Third, when surgical intervention does become necessary, contemporary minimally invasive options achieve durable control while permitting continued intravitreal corticosteroid therapy.³⁵

Cataract is best regarded as an anticipated consequence rather than a complication. Its incidence is a direct function of cumulative corticosteroid exposure, rising from 14.5 % after a single implant at 26 weeks to 38–46 % after two to three years of repeated implantation. The clinical implications are practical: phakic patients should be counselled at the outset that lens extraction is a probable eventual requirement; phacoemulsification should be planned electively rather than reactively; and the data of Larochelle and colleagues indicate that administering the implant within four weeks before cataract surgery prevents peri-operative recurrence of macular oedema, with a mean change in central macular thickness of $-47.0\ \mu\text{m}$ compared with $+51.1\ \mu\text{m}$ when the interval exceeded four weeks ($P = 0.005$).^{10,26,33,43}

Serious adverse events were rare in absolute terms. Two cases of endophthalmitis across approximately 1 871 eyes and several thousand injections give a per-eye incidence of 0.11 %, consistent with the background rate for intravitreal injection in general. Anterior chamber migration of the implant is essentially confined to aphakic or vitrectomised eyes with a compromised posterior capsule and is preventable by appropriate case selection and injection technique.^{15,43,52}

Prognostic implications

The exploratory prognostic analysis has an important negative message and a modestly encouraging positive one. The negative message is that no single baseline variable discriminates responders from non-responders with any useful accuracy: the best univariable area under the curve, for baseline central macular thickness, was only 0.593, and prior vitrectomy and lens status were essentially non-discriminatory in isolation. The positive message is that a multivariable construct combining seven routinely obtainable variables achieved an area under the curve of 0.734 with excellent calibration, suggesting that a properly derived and externally validated clinical prediction rule for this indication is feasible and would be clinically useful.^{20,57,59}

The individual predictors are biologically coherent. A greater baseline thickness predicts a larger absolute reduction simply because there is more fluid to remove, an inference confirmed independently by the meta-regression ($R^2 = 68.2\%$; $P = 0.006$). Longer oedema duration predicts a poorer response because chronic cystoid change produces irreversible Müller cell and photoreceptor loss. Epiretinal membrane both mechanically opposes retinal reapposition and shortens the time to recurrence, as Khurana and Porco demonstrated directly. Disruption of the external limiting membrane and ellipsoid zone is the single most powerful negative structural predictor, present in 89.3 % of non-responders in the analysis of Abu Arif and colleagues, and prior pars plana vitrectomy accelerates intravitreal drug clearance. These considerations converge on a clear clinical recommendation: the implant should be deployed early in the course of refractory macular oedema, before chronic structural change forecloses the possibility of functional recovery.^{20,57,59,60}

Implications for clinical practice

Six practical recommendations follow directly from the pooled estimates. The implant should be considered the intraocular agent of first choice for uveitic macular oedema that has failed conventional therapy, on the basis of randomised superiority over methotrexate, ranibizumab and periocular triamcinolone and non-inferiority to intravitreal triamcinolone. Re-treatment should be planned pre-emptively at approximately four to five months rather than delayed until symptomatic recurrence, because the pooled trajectory shows measurable anatomical rebound from month 3 and because half of all eyes recur within six months. Intraocular pressure must be measured at two weeks, six weeks and then at least every two months after each implant, and at every visit in eyes

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with pre-existing glaucoma. Phakic patients should be counselled about cataract at the outset, and where cataract surgery is anticipated the implant should be administered within four weeks before the procedure. In eyes requiring three or more implants within eighteen months, and particularly in pseudophakic eyes that have already demonstrated an acceptable pressure response to dexamethasone, transition to a 0.19 mg fluocinolone acetonide insert should be considered. Finally, in bilateral disease or where extraocular manifestations are present, systemic biologic therapy should be evaluated in parallel rather than deferred.^{12,13,44,55,58,65}

Strengths of this review

The review has several methodological strengths. Its scope is the widest yet applied to this question, encompassing 35 reports and 1 871 eyes across thirteen pre-specified outcome domains, compared with the two to four domains and 201 to 447 eyes of previous syntheses. Every citation was independently verified in an external academic index before inclusion, eliminating the risk of spurious or misattributed references. Risk of bias was assessed with the design-appropriate contemporary instrument in every case, and the certainty of evidence was formally rated with GRADE for all twelve pooled domains. The temporal modelling of the treatment effect across three separate time points, the reconstruction of recurrence-free survival, and the receiver operating characteristic evaluation of baseline predictors are, to our knowledge, novel contributions to this literature. Heterogeneity was not merely reported but explained, with a single covariate accounting for more than two thirds of the between-study variance in the principal anatomical outcome.^{45,46,67}

Directions for future research

Four priorities emerge. A randomised trial comparing pre-emptive fixed-interval re-implantation at four months with reactive re-implantation on recurrence would resolve the single most consequential unanswered management question and could be conducted within existing uveitis networks. An individual-participant-data meta-analysis of the existing cohorts would permit derivation and external validation of a genuine clinical prediction rule for anatomical and functional response, replacing the exploratory construct presented here. Head-to-head randomised comparison of the dexamethasone implant with the 0.19 mg fluocinolone acetonide insert, powered for recurrence and for pressure-related morbidity over three years, would define the optimal sequencing

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of the two devices. Finally, future studies should incorporate patient-reported outcome measures, microperimetric macular sensitivity and optical coherence tomography angiography metrics of the deep capillary plexus, so that the benefit of the implant can be characterised in terms that reflect the patient's visual experience rather than retinal thickness alone.^{13,44,55,65}

CONCLUSION AND RECOMMENDATIONS

Conclusion

In eyes with macular oedema secondary to non-infectious uveitis that has proved refractory to conventional topical, periocular, systemic or anti-vascular endothelial growth factor therapy, the 0.7 mg biodegradable intravitreal dexamethasone implant produces a statistically significant, clinically substantial and highly reproducible therapeutic effect. Central macular thickness falls by a pooled mean of 156.8 μm at one month, 146.2 μm at three months and 101.1 μm at six months, and best-corrected visual acuity improves by 0.160, 0.186 and 0.141 logMAR at the same time points — equivalent to gains of approximately eight, nine and seven ETDRS letters — with every pooled estimate significant at $P < 0.0001$ and with complete absence of heterogeneity in the functional domain. Complete resolution of macular oedema is achieved in approximately four fifths of eyes, a gain of at least fifteen letters in one third, and a vitreous haze score of zero in nearly three quarters. Randomised evidence confirms superiority over sham, over periocular triamcinolone acetonide, over intravitreal methotrexate and over intravitreal ranibizumab, and non-inferiority to intravitreal triamcinolone acetonide.^{10,12,13,14}

The effect is, however, intrinsically time-limited. Median time to recurrence clusters between six and nine months, approximately half of all eyes require re-implantation within six months, and cumulative implant exposure of two to three devices over two to three years is the norm in chronic disease. Safety is dominated by two predictable and monitorable events: clinically significant intraocular pressure elevation in approximately one fifth of eyes, almost always controlled medically and requiring surgery in fewer than 1 %, and cataract progression in approximately one quarter of phakic eyes, rising with cumulative exposure. Vision-threatening complications, including endophthalmitis and retinal detachment, are genuinely rare. Response is multifactorially determined; no single baseline variable predicts it usefully, but a multivariable

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construct incorporating baseline thickness, oedema duration, epiretinal membrane, outer retinal band integrity, lens status, prior vitrectomy and age achieves acceptable discrimination (area under the curve 0.734).^{20,35,43,57}

The certainty of the evidence is high for the two principal safety outcomes, moderate for the anatomical outcomes at months 1 and 3, for all functional outcomes and for inflammatory control, and low for the month-6 anatomical outcome, for complete resolution and for the re-implantation requirement. The alternative hypothesis is accepted in full.^{70,71}

Recommendations for clinical practice

Deploy the dexamethasone implant early in the course of refractory uveitic macular oedema, before chronic cystoid change, epiretinal membrane formation and disruption of the external limiting membrane and ellipsoid zone foreclose the possibility of functional recovery.^{20,57}

Regard the implant as the intraocular agent of first choice for inflammatory macular oedema failing conventional therapy, on the basis of randomised superiority over methotrexate, ranibizumab and periocular triamcinolone and non-inferiority to intravitreal triamcinolone.^{12,13,14}

Plan re-treatment pre-emptively at approximately four to five months rather than waiting for symptomatic recurrence, because anatomical rebound is measurable from month 3 and half of all eyes recur within six months.^{15,20,31}

Measure intraocular pressure at two weeks, six weeks and thereafter at least every two months after each implant, and at every visit in eyes with pre-existing glaucoma or ocular hypertension; these conditions warrant intensified surveillance, not avoidance of the implant.³⁵

Counsel every phakic patient at the outset that cataract extraction is a probable eventual requirement, and where cataract surgery is anticipated, administer the implant within four weeks before the procedure to prevent peri-operative recurrence of macular oedema.^{10,26}

In eyes requiring three or more implants within eighteen months — particularly pseudophakic eyes that have already demonstrated an acceptable intraocular pressure response to dexamethasone — consider transition to a 0.19 mg fluocinolone acetonide insert, using the dexamethasone implant as a corticosteroid-response test.^{44,55,58,65}

In bilateral disease, or where extraocular manifestations are present, evaluate systemic biologic therapy in parallel rather than sequentially, recognising that local and systemic strategies are complementary.^{48,54,64}

Avoid the implant in eyes with active infectious uveitis, and use it with particular caution and close monitoring in aphakic or vitrectomised eyes with a compromised posterior capsule, in which anterior chamber migration may occur.^{15,43}

Recommendations for research

Conduct a randomised trial comparing pre-emptive fixed-interval re-implantation at four months with reactive re-implantation on recurrence, with recurrence-free survival and cumulative letters gained as co-primary endpoints.¹³

Undertake an individual-participant-data meta-analysis of the existing cohorts to derive and externally validate a clinical prediction rule for anatomical and functional response, replacing the exploratory model presented here.^{57,59}

Perform a head-to-head randomised comparison of the dexamethasone implant with the 0.19 mg fluocinolone acetonide insert, powered for recurrence and pressure-related morbidity over three years.^{44,55}

Incorporate patient-reported outcome measures, microperimetric macular sensitivity and optical coherence tomography angiography metrics of the deep capillary plexus into future trials, so that benefit is characterised in terms that reflect the patient's visual experience.¹¹

Standardise the reporting of uveitic macular oedema trials to the SUN criteria, with uniform definitions of refractoriness, of anatomical response and of intraocular pressure events, so that future syntheses are less constrained by clinical and definitional heterogeneity.^{5,67}

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