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Critical Review

Long-term efficacy and safety profile of multiple injections of intravitreal dexamethasone implant to manage diabetic macular edema: A systematic review of real-world studies

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ABSTRACT

Introduction: Systematic review of real-world studies about repeated dexamethasone intravitreal implant (DEXi) 0.7 mg in diabetic macular edema management, in order to identify the effective window of time occurring between injections, the critical evaluation of efficacy of the treatment, and the relative long-term safety in the real life setting.

Methods: Literature databases such as PubMed, SCOPUS, and EMBASE were used to identify reports including DEX implant injections.

Results: Twenty-one peer-reviewed publications were identified. DEX implants retreatment was considered on a *pro re nata* (PRN) basis at any time or starting from month three or four. About 1/3 of the eyes were retreated before six months from first injection (range 0–86.7%). Mean retreatment average time was 5.3 ± 0.9 months, with an estimated average of 1.3 injections each six months. There was no statistical correlation between average retreatment time and incidence of adverse events or other variables investigated. Limited safety issues related to implants number have been found, suggesting an overall good tolerance of long-term DEXi.

Conclusions: Comprehensive evaluation of real-world data suggests an average DEXi duration close to five months, following a PRN treatment strategy, including about 1/3 of patients. Repeated DEXi administration revealed an acceptable long-term efficacy/safety ratio.

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1. Introduction

Diabetic macular edema (DME) represents a major cause of vision loss among working-aged individuals in developed countries.[1] It has been estimated that DME would affect about 20% of individuals with type 1 and type 2 diabetes mellitus after 10 years of disease duration, rising up to 30% after 25 years.[2] Despite the occurrence of vision loss among diabetic patients has decreased over the last decades, the absolute number of individuals with diabetes-related vision loss is rising due to the substantial increase in worldwide diabetes burden.[3] Identification of optimal therapeutic treatment represents therefore a priority for healthcare systems in order to provide patients a better long-term management.[4]

Current advances in research led to significant improvements in understanding DME specific pathogenic mechanisms; there is increasing evidence that inflammatory processes have a considerable role in the pathogenesis of diabetic retinopathy (DR) and DME.[5] Micro-vascular abnormalities occurring in diabetes induce pro-inflammatory and pro-angiogenic processes leading to excessive vascular permeability, leakage of fluid, and finally edema formation; several molecular mechanisms are implicated in DME pathogenesis, including (i) increased expression of the pro-inflammatory molecules such as intercellular adhesion molecule-1 (ICAM-1), tumor necrosis factor-alpha (TNF-α), interleukin-6

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(IL-6), and vascular endothelial growth factor (VEGF); (ii) leukocytes recruitment and adhesion to the retinal vascular endothelium; and (iii) endothelial tight junctions permeability caused by protein loss.[6] For a long time, DME therapeutic alternatives involved laser photocoagulation, which does not specifically address the underlying cause of DME and demonstrated only limited improvement in vision.[7] Another therapeutic option involves intraocular injections of anti-VEGF, characterized by shorter duration of action/higher rate of DME recurrence.[8] Corticosteroids have gained great interest in DME management over the last years as a valid therapeutic alternative, able to being compliant with long-term treatment requirements. In vitro and in vivo studies demonstrated that corticosteroid's anti-inflammatory effect involves changes in the adherence of vascular endothelial cells and therefore the migration of neutrophils through blood vessel walls to inflammation tissue sites, decreasing the amount of macrophages and lymphocytes. Furthermore, these molecules were shown to stimulate the inhibition of phospholipase A_2 and arachidonic acid pathway,[9] to significantly decrease levels of several pro-inflammatory cytokines such as interleukin-8 (IL-8), interferon gamma-induced protein-10 (IP-10), and monocyte chemoattractant protein-1 (MCP-1) and other aqueous permeability factors in patients with DME,[10] and to reduce retinal inflammatory biomarkers as well.[11] As a result of intravitreal administration, steroids bypass the blood-ocular barriers in the eye and decrease vascular permeability during inflammation while minimizing systemic side effects.[12] However, since a single intravitreal injection of dexamethasone in the vitreous humor has a short half-life, intravitreal drug delivery gained interest as an effective method for achieving prolonged exposure and adequate drug concentrations for the treatment of posterior eye disease. Dexamethasone intravitreal implant (DEXi) 0.7 mg (Ozurdex®, Allergan plc, Dublin, Ireland) is a free-floating biodegradable copolymer containing micronized dexamethasone approved for the treatment of DME.[13] Advantages of sustained intravitreal release of dexamethasone include the reduction in the frequency of injections with subsequent lower rates of complications (such as retinal detachment, endophthalmitis, lens iatrogenic injury) related to injection procedure, higher patient compliance and lower healthcare costs.

Several randomized controlled trials (RCTs) demonstrated the clinical efficacy of intravitreal sustained-release dexamethasone implant for DME.[14] Increase in intraocular pressure (IOP) and cataract have been reported as the most common side effects related to DEX implant use.[15] DEX implant received FDA and EMA approval based on MEAD trial results, in which DEX administration was allowed every 6 months and injections mean number over 3 years was 4.1.[16] A more recent study comparing efficacy and safety outcomes of DME patients treated with DEX implant each six months (fixed groups, n = 22) or on an individualized basis (*pro re nata* - PRN group, n = 20) showed a more stable clinical improvement in terms of best-corrected visual acuity (BCVA) and central retinal thickness (CRT) among patients treated at need with a decline in the therapeutic effects at 4–5 month and a complete return to baseline after about 6 months; importantly, no substantial differences in safety between groups were retrieved, as well as most of adverse effects related to IOP (about one third of patients) and cataract.[17] Other results from surveys aiming to monitor the real dispensing of drugs through physicians, pharmacies and social security showed that the average DEX implant injection were 2.4 per year with a time-window between treatment ranging between 4.7 and 5.2 months.[18] In order to strengthen these promising results, further data are needed to corroborate the efficacy and safety of repeated long-term DEX administration in the real-world setting. Up to date, no comprehensive evaluation of repeated long-term DEX administration in the real-world setting has been performed. Thus, the aim of this study was to systematically review existing evidence about repeated DEX implant injections in order to identify the effective window of time occurring between injections, the critical evaluation of treatment efficacy, and the relative long-term safety in the real-life setting.

2. Methods

2.1. Search methods for studies identification

Literature from databases including PubMed, SCOPUS, and EMBASE was analyzed to search current evidence on repeated DEX implant injections, up to October 2017. The search strategy involved the following keywords and Mesh terms: “dexamethasone AND macular AND edema AND intravitreal AND (diabetic OR diabetes)”. Only articles in English were considered for examination. Inclusion criteria for the study selection were the following: (i) involved patients with DME treated with DEX implant; (ii) had an observational/case series design; (iii) evaluated clinical outcomes (efficacy and/or safety) related to DEX implant; (iv) patients were administered at least 2 or more injections of dexamethasone implant. Exclusion criteria were the following: (i) had an experimental design (i.e., RCT); and (ii) case series including less than 10 patients/eyes. Two investigators independently assessed articles for compliance with the inclusion and exclusion criteria and resolved disagreements through consensus.

2.2. Data extraction

The following data was extracted from each study (if available): (i) name of the first author; (ii) year of publication; (iii) country; (iv) inclusion criteria; (v) exclusion criteria; (vi) number of participants/eyes; (vii) sex of participants; (viii) age range or mean age of the study population at baseline; (ix) previous treatments; (x) DEX implant administration design; (xi) follow-up time; (xii) main efficacy endpoints (including BCVA and CRT); (xiii) safety outcomes.

2.3. Assessment of study evidence and risk of bias

The quality of each included study was assessed through the Methodological Index for Non-Randomized Studies (MINORS).[19] Briefly, a list of eight items was scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate): the global ideal score on this scale was 16 for non-comparative studies. Risk of bias for observational studies was assessed following the GRADE guidelines.[20] Briefly, four main domains (including “Failure to develop and apply appropriate eligibility criteria”, “Flawed measurement of both exposure and outcome”, “Failure to adequately control confounding”, and “Incomplete follow-up”) were assessed and graded as 0 (inadequate), 1 (unclear), or 2 (adequate) with a global ideal score of 8 points. Disagreements between the authors were resolved by discussion and/or additional methodologist adjudication.

2.4. Statistical analysis

Due to the heterogeneity of clinical characteristics and design of the studies included, we did not perform a quantitative analysis of the efficacy parameters (BCVA and CRT), rather we reviewed them and discussed in comparison with results from clinical trials. However, we used some descriptive statistics to better summarize the findings among studies. Specifically, mean and standard deviations were used for continuous variables and Pearson's correlation coefficients were used to determine whether correlations occurred between variables.

3. Results

3.1. Study selection

A total of 196 studies were retrieved through search method. 137 studies were excluded based on title and abstract examination (mainly review articles or studies on other therapies or on macular edema of not-diabetic etiology), leaving 59 studies for full-text examination: 13 presented individual cases; 10 did not report data of interest; 8 were conducted on patients undergoing combined therapies; and 5 planned fixed-time retreatments were excluded. Two studies were further excluded because conducted on the same cohort of patients but with shorter follow-up.[21,22] The remaining 21 articles were included in this systematic review (Fig. 1).[23–43]

3.2. Study characteristics

The main characteristics of the studies are presented in Table 1. The studies were mostly conducted in Europe,[23,24,26–29,32,35,36,38,40,41,43] four were performed in Turkey,[34,37,39,42] one in Korea,[33] one in Canada,[25] one in India,[30] and one multinational investigation.[31] Sixteen studies had a retrospective design,[23,25,28,30–40] while five were prospective.[24,26,27,29,41] A total of 831 eyes from 679 patients (average age of 63 years old) treated with DEX implant were examined. Inclusion criteria included adult age, presence of diabetes and diagnosis of DME, and availability of data for retrospective studies; clinical features regarding visual acuity slightly varied among studies, such as BCVA between 20/200 and 20/25 in two studies,[28,31] between 1/10 and 5/10 in three studies,[23,35,36] between 20/320 and 20/40 in two studies,[32,41] and not specified in the remaining ones; in contrast, inclusion criterion interesting central macular thickness (CMT) was mostly ubiquitously >300 μm. Exclusion criteria mainly interested other causes of macular edema, and systemic (i.e., untreated hypertension) or ocular conditions (i.e., uncontrolled IOP) that might have compromised patients' health in case of administration of corticosteroids. Only one study included patients who underwent vitrectomy.[25] Two studies did not report inclusion and/or exclusion criteria.[27,40] Duration of DME ranged between 5.7,[26] and 43 months,[43] with an average of 21.3 ± 13.3 months. Only four studies reported administration of DEX implant therapy to treatment-naïve eyes with no mention to "persistent" DME; most of the remaining studies reported previous treatment with anti-VEGFs (i.e., at least 3 administrations) involving 10–100% of patients, as well as laser treatment and previous intravitreal steroids.[26,28,32,40] However, certain differences regarded the percentage of phakic and/or pseudophakic eyes at baseline, which ranged from 25% to 100%, variously distributed among studies.

3.3. Study quality and risk of bias

Study quality scores ranged from 8 to 14 (Table 1): seven studies scored less than 10 points due to accumulating effect of a lack in high quality criteria, such as prospective data, unbiased assessment, and adequate follow-up.[23,25,30,32,37,38,43] Seven studies clearly stated that data collection was prospective or data "prospectively collected" interesting consecutive patients, while the remaining did not clarified patients' selection.[24,26–28,35,40,41] Five studies[23,29,31,36,42] reported a "no conflict of interest" statement[23,29,31,36,42] and 6 studies also reported (unbiased) funding sources.[26,27,33–35,39]

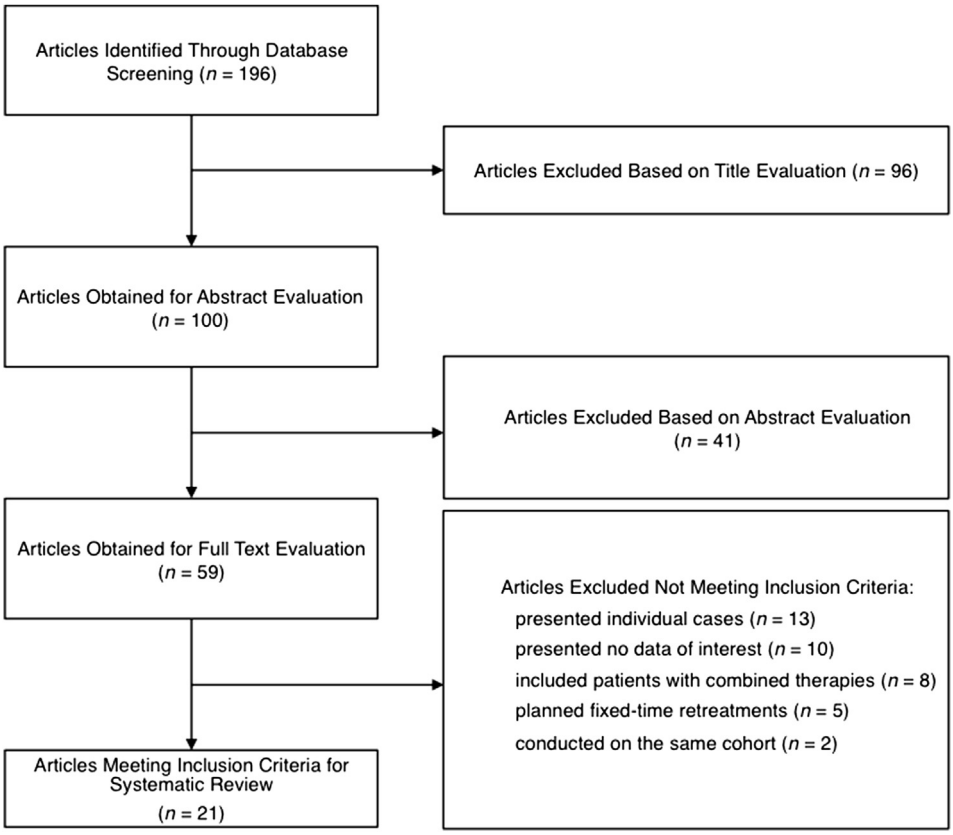

Fig. 1. Flowchart of study selection strategy.

Table 1
Main characteristics of the studies included in the systematic review (n = 21).

Author, year	Country	Study design	Persistent DME	Inclusion criteria	Exclusion criteria	No. Patients/eyes	Patients' age	No. phakic/ pseudophakic eyes	Previous treatments	Duration of DME (months)	DEX retreatment	Study quality	Risk of bias
Pacella, 2013	Italy	retrospective	yes	age >18, a BCVA between 5 (corresponding to 1/10, logMAR 1.0 or more) and 40 (corresponding to 5/10, logMAR 0.3 or less) letters, and CMT >275 mm.	Pregnant, had uncontrolled arterial hypertension, venous occlusions, evolved cataract, glaucoma, an epiretinal membrane visible by optical coherence tomography (OCT), age-related macular degeneration, uveitis, a history of vitreal surgery, cataract surgery (in the previous 6 months), YAG laser capsulotomy (within 2 months prior to the trial), or had undergone recent panreti- nal laser photocoagulation or grid laser photocoagulation (in the 3 months prior to investigation).	17/20	67	NA	Thirteen patients had previously undergone treatment with anti-VEGF or steroids.	NA	Pro re nata from month 4. Criteria: reduced VA (a reduction of logMAR scores of at least 0.2 or 10 letters) and an increase of macular thickness (of at least 150 mm, as measured with OCT).	9	6
Escobar-Barranco, 2015	Spain	prospective	partially	Diabetes and at least one eye with VA between 15 and 72 ETDRS letters and CMT >300 μm as measured by optical coherence tomography (OCT).	Ischemic maculopathy, focal DME, DME associated with vitreomacular traction, corticosteroid responders [a patient with a history of severe IOP increase (>30 mm Hg) after known exposure to intravitreal or drops of corticosteroids], history or presence of branch retinal vein occlusion, central retinal vein occlusion, uveitis or Irvine-Gass syndrome, history of glaucoma or IOP >25 mm Hg, intravitreal treatment with anti-VEGF or photocoagulation within the 3 months prior to patient inclusion, and uncontrolled systemic disease, such as terminal neoplasms, severe neurological diseases or any that could impair a correct follow-up throughout the study.	76/76	65	NA/21	Forty eyes had received a previous laser treatment for retinal panphotocoagulation.	NA	Pro re nata from month 3. Criteria: CMT >150 μm as compared to the lowest value recorded or if there was a loss of more than 10 ETRDS letters with some increase in central thickness.	11	6
Lam, 2015	Canada	retrospective	partially	diagnosis of retinal disease involving ME in the study eye(s); received at least one DEX implant and had follow-up data for a minimum duration of 3 months (12 ± 2 weeks) after the first injection; had data collected from December 1, 2010 through December 1, 2012 inclusive; and had signed an informed consent form prior to first collection of study data.	NA	NA/34	60	11/23	19 eyes had anti-VEGF treatment, 15 had corticosteroids, 23 had previous cataract surgery, 19 had vitrectomy.	>12	Pro re nata at any time. No criteria listed.	8	4
Panozzo, 2015	Italy	prospective	partially	NA	NA	20/20	56	20/0	Eight eyes had previous anti-VEGF and/or laser treatments.	NA	Pro re nata at any time. Criteria: change in VA ≥5 le ers and in FT ≥ 50 μm with respect to the baseline values.	14	5
Scaramuzzi, 2015	Italy	retrospective	no	1) adults (older than equal to 18 years) with controlled diabetes (e.g., blood HbA1c, <9%), 2) the presence of fovea-involving ME secondary to DR in the study eye (including focal or diffuse clinically significant macular edema), 3) BCVA between 20/200 and 20/25, 4) CMT >300 mm as measured by spectral domain optical coherence tomography (SD-OCT), 5) follow-up of at least 6 months after the last Ozurdex injection given, and 6) availability of complete medical records.	1) ME secondary to other causes than DR, 2) the presence of other retinopathies/maculopathies (e.g., retinal vein occlusion (RVO), age-related macular degeneration) or visually significant media opacities (e.g., cataract or corneal opacity); 3) history of ocular trauma or surgery <6 months before the first Ozurdex injection, 4) intravitreal triamcinolone <6 months before the first Ozurdex injection, 5) intravitreal antivascular endothelial growth factor (bevacizumab, ranibizumab, or pegaptanib) < 1 month before the first Ozurdex injection, 6) IOP elevation in response to any previous steroid treatment, and 7) IOP >23 mmHg without antiglaucoma medication, or IOP >21 mmHg with 1 antiglaucoma medication.	12/15	62	9/6	13 eyes of 10 patients (87%) have been undergoing laser photocoagulation of ischemic retina.	32	Pro re nata from month 4. Criteria: 1) fovea-involving intraretinal and/or subretinal fluid, found with fundus biomicroscopy and SD-OCT, which was increased with respect to the peaking efficacy observation; and 2) CMT was higher than 300 mm.	10	7

Mastropasqua, 2015	Italy	prospective	no	1) age >18 years old, 2) presence of DME, 3) BCVA of at least 1.0 LogMAR in the study eye at baseline examination and 4) central macular thickness (CMT) > 300 μm as measured by spectral-domain optical coherence tomography (SD-OCT) at baseline examination.	1) structural damage within a 0.5 disc diameter of the center of the macula in the study eye to not preclude improvement in visual acuity following the resolution of macular edema, including atrophy of the retinal pigment epithelium, subretinal fibrosis, laser scar(s), epiretinal membrane involving fovea or organized hard exudative plaques, 2) any ocular surgery and/or laser treatment in the study eye in the last six months, 3) previous intravitreal injection of corticosteroids or anti-VEGF, 4) a history of ocular inflammation or 5) history of IOP elevation in response to steroid treatment or a history of glaucoma.	27/27	66	NA	All treatment-naive eyes.	5,7	Pro re nata from month 3. Criteria: loss of five letters in BCVA and recurrence/ persistence of macular edema as documented by indirect fundus ophthalmoscopy and SD-OCT (CMT >300 μm).	14	7
Aknin, 2016	France	prospective	partially	Diabetes and at least one eye with VA between 15 and 72 ETDRS letters and CMT >300 μm as measured by optical coherence tomography (OCT).	Ischemic maculopathy, focal DME, DME associated with vitreomacular traction, corticosteroid responders [a patient with a history of severe IOP increase (>30 mm Hg) after known exposure to intravitreal or drops of corticosteroids], history or presence of branch retinal vein occlusion, central retinal vein occlusion, uveitis or Irvine-Gass syndrome, history of glaucoma or IOP >25 mm Hg, intravitreal treatment with anti-VEGF or photocoagulation within the 3 months prior to patient inclusion, and uncontrolled systemic disease, such as terminal neoplasms, severe neurological diseases or any that could impair a correct follow-up throughout the study.	29/29	66	15/NA	Six patients had anti-VEGF treatment.	NA	No criteria listed.	11	5
Matonti, 2016	France	retrospective	no	Treatment with at least 2 injections of Ozurdex and followed for at least 12 months; the BCVA in the studied eye, using the ETDRS method, was required to be between 25 letters (20/320 or 0.06) and 70 letters (20/40 or 0.5) with edematous diabetic maculopathy and without tractional or ischemic maculopathy; CRT measured by SD-OCT had to be ≥ 350 μm.	HbA1c >10% and BP > 160/100 mm Hg; for non-naive patients, the last anti-VEGF injection <2 months before, for triamcinolone injection <6 months before, and for macular laser <6 months before; IOP >25 mm Hg or unbalanced glaucoma.	23/23	66	NA/15	10 (43.5) anti-VEGF; 9 (39.1) triamcinolone acetonide; 10 (43.5) grid laser	NA	Pro re nata at any time. Criteria: DME ≥300 μm on SD-OCT or a loss ≥5 letters (ETDRS).	9	7
Moon, 2016	Korea	retrospective	partially	(1) a diagnosis of type 1 or 2 diabetes and (2) center-involved DME treated with one or more intravitreal DEX implants and followed up for at least 6 months.	ME (1) secondary to other retinal diseases such as retinal vein occlusion, uveitis, or pseudophakic cystoid ME and (2) accompanied by epiretinal membrane with tractional component or vitreomacular traction syndrome.	165/186	57	112/64	29 eyes (15.6%) had macular laser treatment, 152 eyes (81.7%) had anti-VEGF therapy and 42 eyes (22.6%) had intravitreal steroid.	17,3	No criteria listed.	10	5
Ozkaya, 2016	Turkey	retrospective	yes	age ≥18 years, a diagnosis of persistent DME defined as experiencing a complete or partial response to any of treatment modalities other than IDI, not having received any intravitreal injections or laser photocoagulation within the previous 3 months, being pseudophakic, and a follow-up time of at least 12 months.	History of retinal disease other than diabetic retinopathy (e.g., age-related macular degeneration, retinal vein occlusion), refractory DME not responsive to any of the previous treatments, cataract surgery within the previous 6 months, YAG laser capsulotomy within the previ- ous month, panretinal photocoagulation within the previous 3 months, a vitreoretinal surface disorder, a history of prior vitrectomy, preexisting glaucoma, a history of an glaucomatous drug use, a history of ocular hypertension, or family history of glaucoma.	43/50	65	NA/50	Panretinal photocoautgulation was performed in 39 eyes. Previous unspecified treatment in all eyes.	11,5	Pro re nata from month 3. Criterion was CRT >150 mm.	11	7

(continued on next page)

Table 1 (*continued*)

Author, year	Country	Study design	Persistent DME	Inclusion criteria	Exclusion criteria	No. Patients/eyes	Patients' age	No. phakic/ pseudophakic eyes	Previous treatments	Duration of DME (months)	DEX retreatment	Study quality	Risk of bias
Pacella, 2016 a	Italy	retrospective	yes	(1) age >18 years old, (2) DME refractory to anti-VEGF therapy, (3) BCVA between 5 and 40 letters in the study eye at baseline examination (to ensure proper execution of functional examination), and (4) CMT <270 μm.	(1) structural damage (including atrophy of the retinal pig- ment epithelium, subretinal brosis, laser scars, epiretinal membrane involving fovea, or organized hard exudative plaques) within a 0.5 disc diameter of the center of the macula in the studied eye precluding improvement in visual acuity following the resolution of macular edema; (2) ocular surgery in the study eye in the last six months; (3) a history of ocular in ammation or (4) glaucoma; and (5) ocular hypertension in response to steroid treatment.	17/19	68	NA	All patients were previously treated with anti-VEGF therapy, 12 patients had panretinal photocoagulation.	NA	Pro re nata from month 3. Criterion was recurrence/ persistence of ME as documented by indirect fundus ophthalmoscopy and spectral-domain OCT.	11	6
Pacella, 2016 b	Italy	retrospective	yes	age >18 y; persistent DME; BCVA between 5 [corresponding to 1/10, logMAR 1.0 or more] and 40 (corresponding to 5/10, logMAR 0.3 or less) letters; CMT <285 mm measured by spectral domain HRA-OCT with a volumetric 512 × 49-scan system.	NA	32/32	66	NA/26	All patients had previously undergone treatment with anti-VEGF or steroids.	41,9	Pro re nata from month 4. Criteria were a reduction of at least 0.2 or 10 letters or an increase of CMT >150 mm.	10	6
Chhablani, 2016	Multinational	retrospective	partially	(1) adults (older than equal to 18 years); controlled diabetes (HbA1c <8%); (2) the presence of center-involving DME in the study eye; (3) BCVA between 20/200 and 20/25; (4) CMT 425 mm as measured by spectral domain optical coherence tomography (SD-OCT); (5) follow-up of at least 1 year after the first Ozurdex injection was administered; and (6) availability of complete medical records including BCVA and SD-OCT throughout the follow-up	(1) subjects with o1 year follow-up after first Ozurdex injection; (2) unavailability of SD-OCT parameters; (3) any other significant concurrent ocular disease in the study eye, which could be the cause of vision loss.	62/79	61	NA/31	55 eyes underwent anti-VEGF treatment, and 33 eyes underwent additional laser grid photocoagulation	NA	Pro re nata at any time. Criteria: fovea-involving intraretinal and/or subretinal fluid found during clinical examination and SD-OCT and/ or in case of CMT higher than 250 microns on SD-OCT scan.	10	7
Bansal, 2016	India	retrospective	yes	(1) Age >18 years or older, (2) Presence of Non-proliferative diabetic retinopathy (NPDR) or adequately managed Proliferative diabetic retinopathy (PDR) with macular edema on Fundus fluorescein angiography (FFA), (3) decrease in visual acuity in the study eye (6/12 or worse) because of macular edema, (4) CMT >300 mm on spectral domain optical coherence tomography (SD-OCT) associated with/without subfoveal serous retinal detachment (SSRD) and/or cystoid macular edema (CME), and (5) a minimum follow-up of 6 months post injection	(1) diagnosis of glaucoma or ocular hypertension or steroid responder, (2) significant cataract, vascular occlusion or any other ocular comorbidity contributing significantly to decreased vision, (3) uncontrolled systemic disease or other comorbidity, (4) Intravitreal bevacizumab/TA injec- tion within last 3 months, (5) DME due to vitreomacular traction on OCT, and (6) Macular ischemia on FFA.	52/67	58	26/41	Prior focal/grid laser photocoagulation was done in all 67 eyes, pan retinal photocoagulation in 22 eyes, intravitreal anti- VEGF in 45 eyes, and TA in 34 eyes.	25,8	Pro re nata from month 1. Criteria: (1) CMT >275 microns along with spongy retinal thickening/intraretinal cystic spaces or SSRD at or within 500 microm of the fovea and/or (2) diffuse leak on FFA.	9	7
Cicinelli, 2017	Italy	retrospective	yes	(1) age ≥18 years; (2) diagnosis of DM, either type 1 or type 2; (3) presence of clinically significant DME according to EDTRS guidelines; (4) BCVA between 20/ 200 and 20/20; (5) CMT ≥300 μm as measured by spectral domain optical coherence tomography (SD-OCT); (6) follow-up of at least 12 months.	(1) macular edema secondary to other causes than diabetic retinopathy (eg, retinal vein occlusion, age-related macular degeneration, postsurgical macular edema); (2) significant media opacities limiting OCT quality (eg, corneal opacity, cataract, vitreous hemorrhage); (3) history of ocular trauma or surgery ≤6 months before the first DEX injection; (4) any other intravitreal corticosteroid administration before DEX injection; (5) intravitreal anti-VEGF (bevacizumab, ranibizumab or pegaptanib) < 1 month before the DEX injection; (6) uncontrolled glaucoma, defined as IOP >25 mm Hg despite antiglaucoma medication in the study eye.	45/45	67	18/NA	All patients had anti-VGEF therapy. Thirteen eyes (11.1%) had received grid macular photocoagulation.	NA	Pro re nata from month 4. Criterion was until stable BCVA was reached.	9	7

Sacconi, 2017	Italy	prospective	partially	(1) adult patients (≥18 years) with controlled diabetes (HbA1C <9%); (2) presence of fovea-involving macular edema secondary to DR in the eye studied; (3) BCVA between 0.3 and 0.0 LogMAR (Snellen equivalent, 20/40–20/20); (4) CMT >300 μm measured by spectral domain OCT (SD-OCT); and (5) a positive history of previous arterial thromboembolic events, such as cerebrovascular accidents and myocardial infarction within 6 months, or problems related to the compliance with monthly therapy and monitoring.	1) presence of any other ocular disorder able to interfere with the clinical assessment (e.g., retinal vein occlusion or age-related macular degeneration); (2) diagnosis of glaucoma or history of IOP elevation in response to steroid treatment; (3) presence of media opacities (e.g., cataract or corneal opacity); (4) presence of ocular trauma or surgery up to 6 months after baseline; and (5) a positive history of previous treatment with intravitreal triamcinolone acetonide up to 6 months after baseline or with anti-VEGF up to 3 months after baseline.	14/14	61	NA	3 eyes (21%) had previous laser treatment for DME, 2 eyes (14.5%) had intravitreal anti-VEGF >3 months before the baseline visit, and 2 eyes (14.5%) had both laser therapy for DME and intravitreal anti-VEGF >3 months before the baseline visit. Prior cataract surgery was performed in 7 patients.	8	Pro re nata from month 1. Criterion was recurrence/ persistent DME demonstrated on OCT scans.	12	7
Esen, 2017	Turkey	retrospective	yes	Macular edema with a CMT >300 lm measured by spectral-domain OCT, despite at least three consecutive monthly ranibizumab injections with no or partial (reduction of CMT less than 50 mm) response.	Diagnosis of glaucoma, elevated intraocular pressure or a history of steroid-induced ocular hypertension, visually significant cataract, the presence of other retinopathies or maculopathies, vitreomacular traction, peripheral ischemia, history of pars plana vitrectomy, and intravitreal anti-VEGF injection or photocoagulation within 3 months prior to the dexamethasone implant treatment in the study eye.	20/25	59	13/12	All eyes had received panretinal laser photocoagulation prior to application. At least three consecutive monthly Anti-VEGF injections.	20,8	Pro re nata at any time. Criteria: CMT increased more than 150 mm as compared to the lowest value recorded or BCVA decreased due to recurrence of macular edema	10	6
Unsal, 2017	Turkey	retrospective	yes	(i) at least three administrations of an intravitreal anti-VEGF drug, (ii) DME persisting beyond 6 months, (iii) CMT ≥300 μm.	eye surgery (except cataract surgery), trauma history, epiretinal membrane or vitreomacular traction in optic coherence tomography, macular ischemia in fluorescein angiography, glaucoma, IOP over 21 mmHg or use of topical and/or systemic steroids within the last 3 months; hemorrhage disorder, active ocular infections, a recent history of myocardial infarction, uncontrolled hypertension or who were pregnant at the time of treatment; eye surgery or who received DME treatment other than a dexamethasone implant, such as intravitreal anti-VEGF, or who underwent photocoagulation during their follow-up.	46/46	61	26/20	All patients were previously treated with anti-VEGF therapy.	>6	Pro re nata at any time. No criteria listed.	10	6
Malcles, 2017	France	retrospective	no	NA	NA	89/128	66	57/71	Anti-VEGF were used in 90 (70.3%) patients, focal/grid laser was used in 21 (16.4%) patients.	24,7	Pro re nata at any time. Criteria: recurrence of DME, defined as the presence of intraretinal cysts on spectral domain optical coherence tomography usually associated with visual impairment.	10	5
Arikan Yorgun, 2017	Turkey	retrospective	yes	Diagnosis of persistent DME despite at least 3 consecutive monthly intravitreal ranibizumab injections	Macular ischemia detected by Fluorescein Angiography, any sign of epiretinal membrane and/or vitreomacular traction on optical coherence tomography (OCT), history of any intraocular surgery, panretinal photocoagulation, and focal/grid laser therapy within 3 months of DEX implantation	28/28	60	7/8	All patients were previously treated with anti-VEGF therapy. Conventional macular laser photocoagulation therapy was applied on 10 patients.	23,4	Pro re nata from month 3. Criteria: (i) incomplete responsiveness (reduction in retinal thickness less than 50 lm without an improvement in visual acuity) or (ii) recurrence of macular edema (increase in macular thickness by more than 20% compared to the last examination after an initial improvement which causes deterioration of visual acuity and/or newly diagnosed fovea-involving intraretinal or subretinal fluid causing visual deterioration).	9	7

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Table 1 (*continued*)

Author, year	Country	Study design	Persistent DME	Inclusion criteria	Exclusion criteria	No. Patients/eyes	Patients' age	No. phakic/pseudophakic eyes	Previous treatments	Duration of DME (months)	DEX retreatment	Study quality	Risk of bias
Zandi, 2017	Switzerland	retrospective	yes	Chronic DME over 6 months without complete resolution despite prior treatment with bevacizumab and/or ranibizumab.	Clinically not sufficiently controlled glaucoma, clear lens in young age, structural damage to the macula excluding functional gain, instable retinal detachment, and any systemic disease interfering with the local situation (ie, systemic vasculitis).	28/34	66	NA/25	All patients were previously treated with anti-VEGF	48	Pro re nata at any time. Criteria: CRT >250 mm and/or a vision loss of more than 5 letters.	9	7

Among the studies, four had a reliably low risk of bias[25,27,33,40]: lower scores were due to lack of reporting inclusion/exclusion criteria and criteria for retreatment with DEX implant (Table 1). All papers failed in detailing reporting adequate control for confounding variables.

3.4. Follow-up and DEX implants retreatment

The mean follow-up ranged from 5.5 to 23 months, with an average of 10.6 ± 4.7 months among all studies.[25,43] Noteworthy, one study had a follow-up up to 18 months but patients number significantly dropped over time (from 29 to 6), thus only results up to 6 months were considered.[29] DEX implants retreatment was considered on a PRN basis at any time or starting from month 3 or 4 in eight studies[25,27,31,32,39,40,42,43] five studies[24,26,34,35,37] and four studies,[23,28,36,38] respectively. Clinical criteria for retreatment were recurrence of DME proved with worsening of BCVA or CRT parameters; however, four studies did not list specific criteria for retreatment.[25,29,33,42]

3.5. Study follow-up and treatment characteristics

Information on study follow-up and treatment characteristics are listed in Table 2. The percentage of eyes retreated before 6 months from first injection ranged from 0[36] to 86.7%,[28] with an average of 37.4 ± 25.6% among studies. Mean time of retreatment ranged from 3.9[43] to 7.3 months,[40] with an average of 5.3 ± 0.9 months between treatments and an estimated average of 1.3 injections each 6 months. There was no statistical correlation between average time of retreatment and any of the variables investigated (patients' age, duration of DME, number of phakic/pseudophakic eyes, length of follow-up, number of retreated eyes, and number of DEX implant injections during the follow-up, and baseline BCVA); however, number of injections was significantly directly correlated with duration of DME ($R = 0.874$, $P = 0.001$).

3.6. Efficacy

Results on efficacy are presented in Table 2. On average, BCVA and CRT parameters were reported for up to 6 months in the majority of studies, while nine studies provided insights for longer follow-up periods,[26,31,32,34,36–38,40,41] and one study provided general results at one month after administration or retreatment.[27] Baseline BCVA and CRT parameters were mostly comparable and did not differed clinically across studies with the exception of one study reporting significant lower values of ETDRS letter[35]; no particular association between efficacy outcomes and severity of DME or persistence has been detected. BCVA and CRT parameters at 6 months significantly improved in five studies[24,28,29,33,35] while the remaining seven studies reporting results for ≤6 months showed peak improvements up to 3–4 months and a non-significant change from baseline after 6 months.[23,25,27,30,39,42,43] Between these two groups there was no difference in percentage of retreated patients (42.3% *vs.* 40%, respectively) nor in time between DEX implant injections (5.1 *vs.* 4.7 months, respectively). Regarding studies reporting results for longer follow-up, eight studies showed a significant improvement in BCVA parameters up to month 9,[31,37] month 12,[32,34,38,41] month 18,[36] and month 36,[40] while one study did not report results for retreated patients (this study showed significant improvements up to month 5).[26] Interestingly, studies reporting results for longer follow-up (>12 months) showed a lower percentage of retreated patients (27.8% *vs.* 32.1%, respectively) and a significant longer time between DEX implant injections compared to those reporting results for ≤12 months (5.2 *vs.* 6.6 months, respectively), which in turn are lower

Table 2
Main results of the studies included in the systematic review (n = 21).

Author, year	Follow-up (months)	No (%) of retreated <6 mo	No. of DEX injections during follow-up	No. of DEX injection per 6 months	Interval between DEX injections (months)	Main results	Side effects and complications
Pacella. 2013	6	2 (10)	1.1	1.10	NA	BCVA changed from 18.8 ± 11.06 letters ETDRS at baseline to 21.25 ± 11.46 at month 6 (P = 0.5). CMT changed from 518.8 ± 224.75 at baseline to 494.25 ± 182.7 at month 6 (P = 0.67).	An increment of IOP was seen in one patient (5.7%) 2 months after the implant (26 mmHg). This condition lasted 2 weeks but was successfully treated with a topical antiglaucomatous medication.
Escobar-Barranco, 2015	6	29 (38.2)	1.9	1.90	4.5	VA changed from 59.6 ± 9.1 letters at baseline to 71.1 ± 9.6 at month 6 among naive eyes, and from 51.3 ± 15.5 at baseline to 59 ± 14.7 at month 6 among refractory eyes (P < 0.001). CTM changed from 569 ± 151.4 at baseline to 323.1 ± 100.8 at month 6 among naive eyes, and from 600.8 ± 163.6 mm at baseline to 281.3 ± 143.8 at month 6 among refractory eyes (P < 0.001).	Six eyes (7.9%) showed a transient IOP increase greater than 10 mm Hg above baseline, all of them controlled with bimatoprost drops. Two eyes (2.6%) belonging to 2 refractory patients out of the 24 with no previous cataract surgery developed cataract which needed phaco- emulsification. Two eyes (2.6%) presented with retinal hemorrhage and 3 (3.9%) with vitreous hemorrhage; out of these latter ones, 1 required vitrectomy.
Lam, 2015	5.5	15 (44.1)	1.6	1.75	5.7	BCVA changed from 0.60 ± 0.03 logMAR at baseline to 0.7 ± 0.5 at last follow-up (P > 0.05). CTM 450 ± 26 at baseline was reduced of −190 ± 23.5 at last follow-up (P < 0.001).	Six patients (17.6%) had increased IOP, 40% of which had IOP increase of at least 10 mmHg and 20% of >25 mmHg.
Panozzo, 2015	12	12 (60)	1.9	0.95	5.2	At month 1 mean VA improved by 19% (mean difference 13.9 ± 5.3 letters, P < 0.05) and mean FT decreased by 43.7% (mean difference −324.9 ± 131.3 μm, P < 0.05).	Six eyes (30%) received topical medication for modest temporary IOP increase (21−24 mm Hg).
Scaramuzzi, 2015	23	13 (86.7)	NA	NA	6.0	BCVA changed from 0.67 ± 0.33 logMAR at baseline to 0.53 ± 0.31 logMAR after a mean of 40.9 ± 18.2 days from the first Ozurdex (peaking efficacy) (P < 0.001), to 0.53 ± 0.29 logMAR after a mean of 34.4 ± 9.0 days from the second Ozurdex (peaking efficacy) (P < 0.003), and stabilized to 0.62 ± 0.26 logMAR after mean of 29.8 ± 12.1 days from the third Ozurdex (peaking efficacy) (P = 0.05), to 0.5 ± 0.26 logMAR after mean of 36.3 ± 3.2 days from the fourth Ozurdex (peaking efficacy) (P = 0.2), and to 0.50 ± 0.26 logMAR after mean of 37.0 ± 2.6 days from the fifth Ozurdex (peaking efficacy) (P = 0.2). Mean baseline CMT significantly decreased from 546 ± 139 mm to 292 ± 43 mm at 39.4 ± 17.9 days from the first Ozurdex (peaking efficacy) (P < 0.001), to 297 ± 47 mm at 33 ± 9.4 days from the second Ozurdex (peaking efficacy) (P, 0.001), to 293 ± 22 mm at 29.8 ± 12.1 days from the third Ozurdex (peaking efficacy) (P = 0.01), and stabilized to 309 ± 35 mm at 36.3 ± 3.2 days from the fourth Ozurdex (peaking efficacy) (P = 0.1), and to 295 ± 7 mm at 37.0 ± 2.6 days from the fifth Ozurdex (peaking efficacy) (P = 0.1).	Three eyes (20%) developed an IOP increase (mean, 20 mmHg) between 1 month and 3 months after injections. Cataract progression was observed in 1 of 9 phakic eyes. A laser or surgical procedure to reduce IOP was not required for any of the study eyes, whereas cataract was extract at the investigator and patient discretion after 18 months from the first Ozurdex injection.
Mastropasqua, 2015	12	15 (55.6)	NA	NA	6.7	BCVA changed from 0.33 (0.19−0.37) at baseline to 0.11 (0.01−0.18) at month 5 (P = 0.022) and 0.21 (0.14−0.30) logMAR at month 12 (P > 0.05). CMT changed from 358 (331−558) at baseline to 284 (233−299) at mont 3 (P < 0.001) and 316 (311−327) at month 12 (P > 0.05). c (results referred only to not retreated patients).	None.
Aknin, 2016	6	14 (48.3)	1.4	1.4	5.6	BCVA changed from 51.7 (10−77) letters at baseline to 65.6 (20−85) letters at month 6 (P < 0.001). CRT changed from 483.2 (300−674) at baseline to 324.2 (163−600) at month 6 (P < 0.001).	Three patients had minor conjunctiva hemorrhages; 2 patients had mild fluid egresses from the sclera wound after injection; 2 patients had an increase in intraocular pressure (≥25 mm Hg, maximum 26); 11 patients underwent intraocular pressure-lowering treatment; 4 phakic patients developed cataracts.
Matonti, 2016	12	3 (13)	2.1	1,05	5.5	BCVA changed from 49.6 ± 16.9 ETDRS letters at baseline to 57.7 ± 13.9 letters at month 6, and 58.3 ± 14.9 letters at month 12 (P = 0.003). CRT changed from 701.6 ± 189.9 μm at baseline to 385.7 ± 172.8 μm at month 12 (P < 0.001).	An increase in IOP was observed in 13.1% of patients. Increase in IOP (≥25 mm Hg) was transient with a maximum at month 2 and was noted in 11.7% of the patients. Ocular hypertonia ≥25 mm Hg was noted in 13% at month 2 and month 8, and only for 4.3% of patients at month 12. A total of 8.7% of the patients had a rise in IOP ≥10 mm Hg at month 2 and none at month 12. Six patients had subconjunctival hemorrhages; 2 patients had Intravitreal hemorrhages.

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Table 2 (*continued*)

Author, year	Follow-up (months)	No (%) of retreated <6 mo	No. of DEX injections during follow-up	No. of DEX injection per 6 months	Interval between DEX injections (months)	Main results	Side effects and complications
Moon, 2016	6	49 (26.3)	1.3	1.3	4.4	BCVA changed from 0.60 ± 0.36 LogMAR at baseline to 0.49 ± 0.37 LogMAR at month 3 ($P < 0.001$) and 0.55 ± 0.38 LogMAR at month 6 ($P = 0.044$). CRT changed from 491.6 ± 164.6 mm at baseline to 357.7 ± 137.7 mm at month 3 ($P < 0.001$) and 412.5 ± 180.8 mm at month 6 ($P < 0.001$).	Eight eyes (4.3%) had an IOP of more than 30 mmHg, and one eye had an IOP that increased to 50 mmHg at 1 month after the DEX implantation. This patient was managed using anterior chamber paracentesis with IOP lowering agents and then maintained a normal IOP range. All of the other patients were managed with one or two IOP lowering agents. In the 112 phakic eyes, 26 (23.2%) eyes showed progression of lens opacity and 7 (6.3%) received lens extraction during the study period. Infectious endophthalmitis occurred in one patient (0.5%).
Ozkaya, 2016	12	10 (20)	2.04	1.02	5.7	BCVA changed from 0.78 ± 0.37 logMAR at baseline to 0.70 ± 0.33 at month 6 ($P = 0.02$) and 0.61 ± 0.34 at month 12 ($P < 0.001$). CRT changed from 606 ± 202 at baseline to 405 ± 149 mm at month 6 ($P < 0.001$) and 397 ± 144 mm at month 12 ($P < 0.001$).	Seven of the 50 eyes (14%) showed an increase in IOP of ≥10 mm Hg and only 2 of them (4%) needed chronic antiglaucoma medication. The IOP increase was transient in the other 5 eyes (10%). Only mild complications like punctate keratitis, subconjunctival hemorrhage, and chemosis were detected.
Pacella, 2016 a	6	2 (10.5)	1.1	1.10	NA	BCVA changed from 19.16 ± 10.9 letters ETDRS at baseline to 21.66 ± 11.24 at month 6 ($P < 0.001$). CMT changed from 508.88 ± 164.05 at baseline to 484.77 ± 167.43 at month 6 ($P > 0.05$).	No particular complications caused by either the implant or the drug itself were found. In addition, none of the eyes showed an increase in intraocular pressure requiring medical treatment.
Pacella, 2016 b	18	0	4	1,33	6.0	At month 6, 12, and 18, ETDRS values were statistically higher than baseline ($P < 0.001$ versus baseline), despite a trend to return to baseline conditions was observed. At month 6 ($P < 0.01$), 12 and 18 ($P < 0.001$), CMT was also significantly lower than T0 although a trend to return to the baseline conditions was also observed (no values were specified).	The IOP values registered during the follow-up did not show significant increments. In 5 patients (15.6%), IOP was higher than 21 mm Hg, and this condition was successfully treated with beta-blocker drugs.
Chhablani, 2016	9	22 (27.8)	1.3	0.87	6.5	BCVA changed from 0.58 ± 0.25 at baseline to 0.44 ± 0.33 logMAR at last follow-up ($P = 0.05$) in naive eyes and from 0.65 ± 0.34 at baseline to 0.48 ± 0.35 logMAR at last follow-up ($P = 0.01$) in previously treated eyes. CMT changed from 550.6 ± 130 mm at baseline to 377.1 ± 105.8 mm at last follow-up ($P = 0.003$) in naive eyes and from 535.3 ± 196.9 at baseline to 413 ± 242.4 mm at last follow-up ($P = 0.01$) in previously treated eyes.	IOP at baseline and at last follow-up was 14.3 ± 3.2 and 15.3 ± 2.8 mmHg, respectively. Three eyes required antiglaucoma medications.
Bansal, 2016	14	26 (38.8)	NA	NA	4.1	BCVA changed from 0.82 ± 0.46 at baseline to 0.68 ± 0.49 logMAR at month 6 ($P = 0.091$). Forty eyes (59.7%) had >2 lines improvement of BCVA, 18 eyes (26.8%) had one line improvement, and 9 eyes (13.4%) had no improvement in visual acuity on Snellen's chart. CTM changed from 514.2 ± 177.87 mm at baseline to 419.9 ± 186.3 mm at month 6 ($P = 0.03$). The maximum decline in CMT from baseline was noticed at 6 weeks after injection in 48 (71.6%) eyes and at 12 weeks in 19 (28.4%) eyes.	The mean IOP changed from 13.4 ± 2.9 mmHg at baseline to 17.0 ± 5.3 mmHg at 6 months. Eight eyes (11.9%) showed a rise in IOP >21 mmHg, out of which 2 eyes had IOP >30 mmHg. Three eyes showed cataract progression after second Ozurdex injection and underwent phacoaspiration with intraocular lens implantation. Mild sub-conjunctival hemorrhage occurred at site of injection in 8 eyes.
Cicinelli, 2017	12	30 (66.7)	1.9	0.95	4.6	BCVA changed from 64.2 ± 22.2 letters at baseline to 69.9 ± 21.9 letters at month 4 and 68.1 ± 25.3 letters at month 12 ($P = 0.05$). CTM changed from 531.9 ± 168.8 mm at baseline to 367.3 ± 111 mm at month 4 and 350.8 ± 90.9 mm at month 12 ($P < 0.001$).	Seven eyes (18.4%) developed IOP ≥20 mm Hg after DEX injection, and these patients were successfully treated with topic antiglaucoma medications. Cataract progression was observed in nine among the phakic eyes (50%) during the study period, and two patients underwent cataract extraction after the DEX injection.
Sacconi, 2017	12	1 (7.1)	1.7	0.85	5.8	BCVA changed from 0.25 ± 0.05 LogMAR at baseline to 0.10 ± 0.08 LogMAR at month 12 ($P < 0.001$). CTM changed from 484 ± 127 μm at baseline to 311 ± 51 μm at 12 month ($P < 0.001$).	Three eyes (21%) developed IOP elevation >21 mm Hg (mean 24.0 ± 1.5 mm Hg), which was successfully managed with topical IOP-lowering medication.
Esen, 2017	6	13 (52)	1.9	1.90	4.4	BCVA changed from 0.97 ± 0.26 logMAR at baseline to 0.85 ± 0.31 logMAR at month 4 ($p = 0.014$) and 0.89 ± 0.31 logMAR at month 6 ($p = 0.15$). CMT changed from 616 ± 132 mm at baseline to 420 ± 116 mm at month 4 ($P < 0.001$) and 494 ± 128 mm at month 6 ($P < 0.001$).	Four (16%) eyes developed a transient intraocular pressure increase (21 mm Hg) that was managed with topical anti-glaucoma medication. No eyes necessitated glaucoma surgery. Progression of lens opacities, which did not yet require surgery, was observed in one (4%) eye.

Unsal, 2017	8.95	4 (8.7)	1.1	0.74	NA	BCVA changed from 0.88 ± 0.3 at baseline to 0.83 ± 0.29 at month 4 (P = 0.027) and 0.85 ± 0.28 at month 6 (P = 0.063). CMT changed from 498.1 ± 90.7 at baseline to 486.0 ± 87.9 at month 3 (P = 0.039) and 489 ± 82.3 at month 6 (P = 0.760).	Eight eyes had an IOP >25 mmHg in the month following injection. All of these patients' IOP values decreased to within normal limits (<22 mmHg) after administration of topical antiglaucomatous drugs and did not require surgery. Subconjunctival hemorrhage occurred after 6 of the 50 injections (12%) given to patients. Four patients were diagnosed with cataracts in month 11 and two of these patients underwent cataract surgery.
Malcles, 2017	16	NA	3.6	1.35	7.3	BCVA improved to 54.7 (95% CI, 50.7−58.7) letters (20/80) at Month 12, 56.0 (95% CI, 51.4−60.6) letters (20/80) at Month 24, and 60.6 (95% CI, 52.0−69.2) letters (20/63) at Month 36. This corresponded to a mean gain from baseline of +4.2 letters at Month 12 (P = 0.006), +5.3 letters at Month 24 (P = 0.007), and +9.5 letters at Month 36 (P = 0.023). Mean CMT decreased statistically significantly to 370 mm at 12 months (P < 0.001), 377 mm at 24 months (P = 0.004), and 280 mm at 36 months (P = 0.001)	IOP >25 mmHg, at any visit during the study, was observed in 10.2% (n = 13) of eyes. An increase of 10 mmHg or more from the baseline was found in 19% of eyes (n = 24). Ocular hypertonia of >35 mmHg was observed in 2.3% (n = 3) of eyes. Intraocular pressure elevation required topical IOP-lowering medication in 21% (n = 27) of eyes. No additional procedures (laser or surgery) were required to normalize IOP. Cataract surgery was performed in 47% of the phakic eyes (n = 27/57). Retinal neovascularization was observed in two cases during follow-up.
Arikan Yorgun, 2017	10	15 (53.6)	2.5	1.50	4.3	BCVA changed from 0.83 ± 0.29 at baseline to 0.67 ± 0.31 logMAR at month 9 (P = 0.041). CMT changed from 561 ± 124.9 mm at baseline to 333.1 ± 137.1 mm at month 9. b (all results referred only to retreated patients)	Six patients used IOP-lowering medication, 4 patients had IOP levels >25 mmHg and 1 patient >35 mmHg; those patients were successfully treated with topical anti-glaucoma treatment. None of the patients underwent glaucoma surgery to control IOP. One of the phakic patients developed cataract that necessitated cataract surgery after the end of follow-up period.
Zandi, 2017	23	28 (82.4)	5.8	1.51	3.9	BCVA (ETDRS letters) changed from 69 ± 20 before the first injection of dexamethasone to 81 ± 14 (P = 0.007) 3 months later and to 76 ± 20 before the first reinjection (P = 0.15). CRT changed from 534 ± 208 at baseline to 287 ± 115 mm by the 3-month follow-up (P = 0.02) before increasing again to 460 ± 192 mm by the time of the first reinjection and decreasing once more substantially after each reimplantation.	IOP changed from 13.4 ± 3.8 at baseline to 17 ± 5.6 at month 3 (P = 0.34) and plateaued at a level of 14 ± 2.9 by the time of the first reinjection. In 2 vitrectomized eyes, a leakage from the injection site resulted in hypotony, requiring an injection of air to restore a normal IOP level. Rises of IOP were medically controlled by the administration of no more than 2 antiglaucoma agents in 11 eyes.

than results presented in studies with ≤6 months follow-up. These results suggest that longer treatment with DEX implant would improve treatment clinical efficacy, stabilizing the DME and prolonging the effects with a better VA.

3.7. Safety

Results on safety are presented in Table 2. Overall, there were no relevant differences in frequency and type of adverse events among studies in relation with treatment features; however, two studies reported no adverse events.[26,35] The most common safety issues reported were IOP rise and cataract occurrence. In most of studies, IOP rise interested about <20% of patients/eyes, while one study reported slightly higher rates (30%, comprising 6 patients).[27] Most of the IOP rise cases were managed with IOP-lowering agents and anti-glaucoma medications; none required surgery procedures. Cataract-related complications occurred in around 50% of phakic patients in two studies,[33,38,40] while interested only a minority of patients (<10%) in other eight studies.[24,28–30,37,39,42] Other mild complications in minimal percentage of patients (1–2%) have been reported, including retinal/vitreous/subconjunctival hemorrhage in five studies[24,30,32,34,42] or retinal neovascularization in one study.[40]

4. Discussion

In this systematic review of real-life studies, evidence suggests that repeated DEX implant injections are effective in ameliorating clinical features of DME especially with “at need” long-term treatment strategy. Moreover, data from the studies with a longer follow-up (>12 months) showed that an earlier DEX implant retreatment (with an average of 5.3 ± 0.9 months) may results in a more effective DME stabilization, requiring fewer retreatments thereafter. Limited safety issues related to the number of implants received have been found, suggesting an overall good tolerance of the drug for chronic treatments and unaltered profile of the DEX implant after retreatment interval reduction.

Regarding repeated DEX implant injections efficacy in term of vision improvements, evidence showed a treatment effect measured by improvement in BCVA, especially in studies with longer follow-up. Likewise, decrease in CRT was improved after repeated DEX implant treatments. The MEAD trial showed that more than 20% of patients treated with 0.7 mg DEX implant (n = 351) improved >15 ETDRS letters from baseline.[16] Mean average reduction in CRT from baseline was greater with DEX implant 0.7 mg (−111.6 μm) than in the other groups.[16] These results are confirmed by a 3-year real-life study where the proportion of eyes achieving at least a 15 ETDRS letters improvement from baseline was 25.4% and the mean reduction was 171 μm at month 36.[38] These data are in line with findings from RCTs in which repeated DEX implant administrations were planned by protocol in a window of time shorted than 6 months. For instance, in a RCT in which DEX implant was administered at baseline, Month 5 and Month 10, authors reported that about 27% of patients (out of 181) showed more than 15-letter BCVA after treatment with repeated DEX implant over a 12-month follow-up.[44] Similar results were obtained in a RCT conducted on patients with persistent DME: after DEX implant administration at baseline, Month 3 and Month 6, about 30% of eyes (out of 27) gained 10 BCVA (ETDRS letters), 15% more than 15 letters and reduction of CRT (−108 μm).[45] In another RCT, re-treatment with DEX considered each 4 months from baseline with a follow-up of 12 months showed a gain of 10 letters of more in 41% (out of 46 eyes) and a mean change in CMT of −187 μm in patients treated with DEX implant.[46]

Concerning safety, the most common reported adverse event was IOP elevation that ranged between 10% and 20%, often occurring soon after the injection, irrespective of previous treatments number. The majority of studies reported that most patients were successfully managed with IOP-lowering medication and none required a surgical procedure to reduce IOP. Results are generally consistent with those reported in the MEAD trial: an average of 30% of patients with 0.7 mg DEX implant reported increase in IOP >10 mmHg from baseline; mean IOP peaked at 1–3 months after DEX implant injection, and was highest after the initial DEX implant injection rather than after subsequent injections, and unrelated to the total number of injections received. Furthermore, there is no evidence for a cumulative effect of multiple injections on IOP.[47] IOP-lowering medication was used at some point during the study by about 40% of DEX implant-treated patients and was usually sufficient to overcome the IOP; only 0.3% of patients required incision glaucoma surgery.[47] Referring to RCTs in which DEX implant re-treatment was more frequent than each 6 months, IOP-related adverse effects were reported in about 40% of patients in the DEX implant group; the same percentage of patients used IOP-lowering medication in the study eye.[44] In another RCT, about half patients (out of 27 eyes) reported IOP >21 mmHg in at least one visit, but none of the eyes required laser or incisional surgery for glaucoma.[45] Previous RCT with repeated DEX implant administration showed an IOP elevation by at least 5 mmHg from baseline at any follow-up visit in 46% (out of 46 eyes), 12 of which demonstrated an IOP of more than 25 mmHg at least once during the 1-year follow up. Eyes with IOP increases were successfully managed with either observation or topical IOP-lowering medications.[46] Results from a study aimed to analyze the pressure tolerance of DEX implant in real-life showed that the number of patients with ocular hypertension decreased over the course of the follow-up period as patients received more DEX implant, and in patients retreated between 3 and 4 months after the previous injection no additional risk of pressure elevation was found compared with a time to retreatment >4 months.[18] Incidentally, it is noteworthy that intraocular pressure can be modulate by corticosteroids in opposite directions,[48] and novel selective glucocorticoid receptor agonists were recently explored to avoid side effects,[49] even though no molecule has been approved so far to clinical use.

Among other side effects, rates of cataract-related adverse events have been reported to be around 60% of treated patients in the MEAD trial.[16] The incidence of cataract-related adverse events in the DEX implant group was slightly lower in another RCT (about 40%).[44] In another study, cataract surgery was registered in 7% out of 27 eyes treated with repeated DEX implant in a 7-month RCT.[45] In a previous RCT, 6.5% out of 46 eyes treated with repeated DEX (PRN regimen starting from month 4) required cataract surgery during the 12-month study.[46]

Regarding systemic adverse events, studies included in this systematic review reported sporadic cases demonstrating DEX implant was generally well tolerated. Also data from RCT with repeated DEX implants more frequent than each 6 months showed small or no effects at systemic level: the most frequent adverse effects were hypertension worsening,[46] and general systemic effects[45] involving less than 1% of the patients involved in the trials.

The role of corticosteroids in DME treatment has emerged as crucial in supporting the need for long-term and multifactorial treatments in patients. The differences in length of efficacy (i.e., need for re-treatment with DEX before 6 months) and adverse events related to corticosteroid use may depend on clinical conditions of patients before DEX administration and their level of response to other treatments. Patients recruited in the real-world setting may have different baseline characteristics, with particular reference to the clinical differences in treatment-naïve patients and those refractory to laser (or other previous treatments). The lower level of irreversible retinal damage between naïve patients

might explain why these patients have a more favorable prognosis as compared with previously treated patients. Furthermore, mean time to retreatment is statistically longer in naïve eyes compared with non-naïve eyes (7.1 months in the first year, 9.5 months in the second year, 15.1 months in the third year).[38] This hypothesis may, at least in part, reflect the findings of the present study: in fact, when comparing retreatment rates, there was no significant correlation between persistent DME or previous treatment occurrence across studies, as well as baseline clinical features, while a significant correlation between number of injections and duration of DME has been found. Such information may suggest that, irrespectively of the patient's clinical condition, longer term DME requires a longer intervention to stabilize the effects of the therapy (explaining also why short-term studies did not show clinical improvements compared to longer-term ones). Thus, reaching the optimal efficacy outcome may not depend on the timing and frequency of injection itself, rather on the early stabilization and maintenance of the clinical condition of the patient, which would benefit in the longer period of a PRN treatment strategy.

The findings reported in this study should be considered in light of some limitations. First, the evident heterogeneity of populations included in the studies reviewed did not permit quantitative comparisons and may weaken the overall comparability of the studies itself. Second, the main results rely on studies using different design; irrespectively of the general study quality, retrospective studies provide lower level of evidence and may be affected by unmeasured or uncontrolled bias (i.e., retrospective research may tend to miss side effects). Third, quality and bias assessment has been performed, but some limitations have been recorded (i.e., potential unmeasured confounding factors).

5. Conclusions

In conclusion, there is need of drug regimens that require a better long-term compliance, including fewer clinical appointments and fewer injections number, in order to minimize adverse events related to such procedure (e.g. endophthalmitis) and limit healthcare costs. The important role played by inflammation in DME pathogenesis represents the rationale for its treatment by intravitreal steroids. Compared to other treatments (i.e., anti-VEGF), DEX implant promises to extend duration of DME management. The comprehensive evaluation of existing data from real-world setting presented in this study suggests an average duration of action close to 5 months following a PRN strategy of treatment interesting about one third of patients, probably depending on their clinical condition DME-related. Retreatment interval reduction does not affect the safety profile of DEX implant. Earlier retreatment with DEX implant (<6 months) may result in a more effective stabilization of DME and less retreatments thereafter. The use of repeated DEX implant administration revealed an acceptable balance between long-term efficacy and safety.

Conflict of interest

The authors declare no conflict of interest.

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