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A review of ten years of experience using dexamethasone intravitreal implants (Ozurdex) for uveitis

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Abstract. – Uveitis is a type of ocular inflammatory disease caused by various etiologies, for which corticosteroids are the main treatment. Dexamethasone Intravitreal implant (DEX-I) has been widely used in the treatment of uveitis across the world. Then, new indications and complications appeared. This review aims to summarize the use of DEX-I in uveitis in the past 10 years.

We summarized the clinical data (baseline characteristics, efficacy and safety) and discussed controversies by retrospectively analyzing the articles and cases published in PubMed and Web of Science using the terms "Ozurdex", OR "intravitreal dexamethasone implant", AND "uveitis" from 2010 to 2022.

DEX-I is effective in reducing edema, improving inflammation and improving vision when treating various conditions of uveitis including infectious, no-infectious, pediatric uveitis, and surgery-related applications. The efficacy of DEX-I as a monotherapy is related to the following: etiology and course of disease, treatment of systemic diseases, patients' toleration after multiple injections, economic situation, etc. In addition, intravitreal corticosteroids implantation may replace systemic therapy in some patients. In terms of safety, the incidence of high intraocular pressure is about 20.52%, and the incidence of cataract is about 15.51%.

DEX-I can effectively treat non-infectious uveitis and some infectious uveitis such as suspected tuberculosis, and its safety is controllable. Further studies are necessary to evaluate the effect of monotherapy and to expand more indications.

Key Words:
Dexamethasone intravitreal implant, Uveitis, macular edema, Systemic therapy, Inflammation, Immunotherapy.

Introduction

Various inflammatory conditions of the eye are classified as uveitis. It involves inflammation of the iris, ciliary body, and choroid, but also adjacent structures, such as the retina, optic nerve, and retinal blood vessels[1-3].

An infection, autoinflammation, or autoimmune condition may cause uveitis[1,4]. Several factors contribute to uveitis epidemiology globally, such as genetics, ethnicity, environment, and socioeconomics. There is a higher prevalence of Behcet's disease, sarcoidosis, and Vogt-Koyanagi-Harada disease in the Asia-Pacific region, while panuveitis is common in northeast China, particularly Vogt-Koyanagi-Harada disease, Behcet's disease and sympathetic ophthalmitis[4,5]. The prevalence of uveitis was 204 per 100,000 persons during 1945-1954 in Rochester, Minnesota. However, it increased to 540 per 100,000 subjects from the National Health and Nutrition Examination Survey (NHANES) in 2018. While the incidence of uveitis was 25 per 100,000 persons per year[6,7]. People between the ages of 20 and 50 are most likely to suffer from uveitis attacks[5,8]. An article[9] in 1996 showed that it can cause 35% of blindness or visual impairment, and recent articles[2] have shown that the United States and Europe account for up to 20% of legal blindness, and developing countries as high as 25%, suggesting that aggressive treatment can reduce blindness from uveitis.

The first line treatment for noninfectious uveitis is systemic corticosteroids or combined with immunosuppressive agents. However, side effects from systemic use are a burden to patients. With the recent advancement of materials science and the precision of treatment, the use of corticosteroids is not limited to oral and intravenous injections[10,11].

Dexamethasone intravitreal implant 0.7 mg (Ozurdex), the biodegradable, sustained release implant, was developed to deliver dexamethasone to eye posterior tissues and the U.S. Food and Drug Administration approved Ozurdex for treating the inflammation of the eye. In the retina and vitreous, dexamethasone concentrations peak

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after 1-2 months and last up to 6 months after the treatment[12,13]. This treatment modality greatly reduces the side effects of corticosteroids due to the small number of corticosteroids in peripheral blood. Previous reviews[14-17] have described the use of Ozurdex in uveitis, showing good results. However, they are all limited to analyzing the efficacy of treating macular edema in adults. The current study will review the use of Ozurdex in uveitis globally over the past 10 years, focusing on indications and etiologies, short- and long-term outcomes in treating macular edema, changes in inflammatory markers, changes in systemic therapy, some special studies (childhood uveitis, surgery-related use, effects on the fellow eye), complications, and a discussion of the efficacy of dexamethasone intravitreal implant as monotherapy (without concomitant systemic therapy).

Research Methods

The terms "Ozurdex", OR "intravitreal dexamethasone implant", AND "uveitis" were searched in PubMed and Web of Science between 2010 and 2022. All published papers about Ozurdex and uvieitis were included along with additional articles based on those papers. Inclusion criteria: all articles related to the therapy of DEX-1 on uveitis. Exclusion criteria: articles containing retinal vein occlusion, diabetic retinopathy quantitatively and qualitatively indistinguishable from uveitis clinical outcomes, editorial, conference and repetition. The initial search revealed 132 articles. Among them, 47 articles were excluded. In total, 85 articles were included in the analysis. The percentage of high intraocular pressure (IOP > 21 mmHg or experienced IOP elevation > 10 mmHg) and cataract (formation or progression) is expressed as n/N% (n: number of high intraocular pressure or cataract, N: total number of eyes receiving DEX injection). All data are from clinical records in the article.

Baseline characteristics (the number of patients/eyes, total injections, average injections, number of re-injections, follow-up time, time to re-injection, course of disease, indications, etiology/ diagnosis), therapeutic effect index [central macular thickness (CMT), best-corrected visual acuity (BCVA), systemic therapy before and after injection] and side effects after injection across all trials were analyzed and tabulated. This review adopts the statistical description of numerical data, does not involve *p*-value.

Etiologies and Indications

We analyzed all selected articles for the top 5 etiologies and indications requiring injections and found that common etiologies include: idiopathic, Behcet's disease (BD), Vogt-Koyanagi-Harada disease (VKH), sympathetic ophthalmitis (SO), pediatric uveitis, sarcoidosis, birdshot chorioretinopathy (BSCR), ankylosing spondylitis (AS), idiopathic intermediate uveitis (IU), juvenile idiopathic arthritis (JIA), tuberculosis (TB), syphilis combined with HIV-positive and so on. Common indications include macular edema (ME), macular edema + vitreitis, macular edema + retinal vasculitis, vitreitis, retinal vasculitis, retinitis, choroiditis, retinochoroiditis, prophylaxis of inflammation and macular edema after intraocular surgery, pre-cataract inflammatory control, prophylaxis of inflammation and macular edema after cataract surgery. However, in 2015, a study[18] examining uveitis specialists' perceptions and practice patterns regarding the use of intravitreal dexamethasone implants in noninfectious uveitis reported that the most frequent indications (clinical finding) were uveitic macular edema, vitritis, non-infectious retinitis/choroiditis, retinal vasculitis and the most associated clinical diagnoses were pars planitis, multifocal choroiditis, birdshot chorioretinitis, sarcoidosis-associated uveitis, Bechet-associated uveitis, HLA B27-associated uveitis, punctate inner choroidopathy, autoimmune retinopathy[18]. It can be seen that with the wide use of DEX-I, its indications are also enriched, especially in infectious uveitis, childhood uveitis and ophthalmic surgery-related applications.

Use of DEX-I in Infectious Uveitis

A case of bilateral tubercular uveitis reported by Hasanreisoglu et al[19] was temporarily improved after anti-tuberculosis treatment and systemic anti-inflammatory treatment, but then the right eye developed vitritis and ME. After a sub-thenon triamcinolone acetonide injection, the vitritis subsided, but the macular edema persisted. Then a single intravitreal dexamethasone implantation was performed. Ten months after the operation, there was no recurrence of macular edema and vitreous inflammation[19]. Fonollosa et al[20] reported a patient with tubercular multifocal serpiginoid choroiditis (TB-associated MSC) in which the lesion was progressing under anti-tuberculosis combined with systemic corticosteroid therapy, which led to the selection of dexamethasone intravitreal implants. After a total of two implants, the progression of inflammation was

successfully controlled[20]. Jain et al[21] summarized that under no objective effect of drug-resistant TB, despite the maximum treatment of systemic corticosteroids, TB-associated MSC seemed to be progressed, or the patient was intolerant to the required dose of systemic corticosteroids, so it was considered to inject a single dose of intravitreal dexamethasone implant. DEX-I was shown to be a safe and effective adjunctive anti-inflammatory therapy for TB-associated MSC patients who cannot take systemic corticosteroids or who need supplemental anti-inflammatory therapy[21]. In TB-associated uveitis, Agarwal et al[22] considered the possibility that systemic corticosteroids and immunosuppressive agents may increase latent TB reactivation, therefore Dexamethasone intravitreal injection was selected. Results showed it could reduce the central macular thickness, vitritis, and progression of choroiditis lesions in paradoxical worsening of MSC[22]. Dutta Majumder et al[23] reported one syphilis patient along with HIV having syphilitic posterior uveitis in the right eye; after intravenous penicillin G together with continued highly active antiretroviral therapy, the cystoid macular edema (CME) secondary to ocular syphilis in the right eye was still and neither periocular corticosteroid nor oral corticosteroid worked in tapering doses. Therefore, the intravitreal dexamethasone implant was selected. After the second injection, the edema and inflammation subsided, and the CD4 count did not decrease compared with that before injection[23]. Before this case, Lautredou et al[24] also reported a case of syphilis with HIV in which the right eye had CME secondary to ocular syphilis. Although actively under treatment, the appearance of the edema was inconsistent with the serological treatment response. Finally, they chose the intravitreal dexamethasone implant; then, the edema subsided postoperation[24]. For other infectious uveitis, so far, only one retrospective study[25] reported that eight eyes with refractory ME secondary to infectious uveitis did not respond to other treatments or recurred easily. Finally, DEX-I was selected, and macular edema disappeared[25]. Therefore, for infectious uveitis, DEX-I is not a first-line treatment. A few studies[19,21,22,25] and reports[20,23,24] suggested that in infectious uveitis DEX-1 should be used with caution in the case of recombinant anti-inflammatory.

The Number of Injections for Different Etiologies and Indications

We selected articles with single etiology or indication to analyze. A study on tuberculous uveitis by Baharani et al[26] did not show the number of injections and then did not participate in this analysis. The results are shown in Table I.

In general, different etiologies often require different injections of DEX. For example, sympathetic ophthalmitis (SO) (average 3 times), BSCR (average 2.67 times) and syphilis + HIV-positive (average 3 times), compared to BD (average 1.1 times), TB (average 1.1 times) and Adult-onset Still's disease (average 1 time), require more injections. Variability is shown for the same indications of different etiologies, such as idiopathic (average 1 time), SO (average 3 times), syphilis + HIV-positive (average 3 times), TB (average 1 time), BD (average 1.18 times), etc., all due to macular edema; variability is also shown for different indications of the same etiologies, for example, in BD and idiopathic, the number of injections is different between only CME and CME combined with various inflammations in the posterior segment. The difference in the number of injections may be partly due to the uniqueness of the disease itself or to the heterogeneity of the disease in different patients, and part of it may be due to the different follow-up time and whether systemic anti-inflammatory therapy is given concurrently. In addition, a study[38] has pointed out that the number of injections is also related to the anatomical type of uveitis. Posterior uveitis and panuveitis are more likely to receive repeated injections[38].

Indications for Re-Injection

Indications for re-injection: 1. CMT > 350 μm (active macular edema); 2. A CMT between 300 and 350 μm and at least one BCVA line was lost; 3. BCVA with an increase of 0.1 logMAR and CMT with a 20% increase (reduction of visual acuity and/or an increase of CMT); 4. BCVA decreases despite a reduction in CMT; 5. Inflammation increasing two steps or from grade 3+ to grade 4+ (anterior chamber relapsed inflammation); 6. the relapse of posterior uveitis[27,31,32,34,39-48]. In addition, a study[49] reported other conditions for multiple implants including: (1) the macular edema was not associated with other pathology such as epiretinal membranes. (2) Earlier injections have treated macular edema without causing serious side effects such as retinal detachment. (3) The patient agreed to have the dexamethasone implant and could afford it[49].

Reasons for not re-injection: inflammation had sufficiently resolved, the disease had stabilized or improved, six months later no improvement was expected and it was too early to consider reinjection at 6 months[48].

Table I. The number of injections for different etiologies and indications.

	Design	Etiology/ diagnosis	Indications	Number of patients/eyes	Follow-up (m)	Total injections (n)	Average injections (n)	Overall average (n)
Yalcinbayir et al[27]	Retrospective and cross-sectional study	BD	CME	20/27	Mean 24.35 ± 9.86 m	32	1.18	1.1
Fabiani et al[28]	A retrospective review	BD	Only CME in 1 eye, CME±active retinal vasculitis in 4 eyes	5/5	At least 6 m	5	1	
Coskun et al[29]	Retrospective study	BD	ME in 5 eyes, leakage of the retinal vasculature in 9 eyes, leakage of the optic disc in 3 eyes	12/17	12 m	17	1	
Kim et al[30]	Retrospective analysis	Sarcoidosis	Intractable vitritis (10 of 20 patients), 6 patients used the implant to improve CME, and 4 patients used the implant to control vasculitis, Systemic corticosteroids and immunosuppressants were not tolerated in 2 patients	20/24	Median 16.5 m	35	1.46	1.42
Myung et al[31]	Retrospective chart review	Sarcoidosis	Papillitis and retinal vasculitis	1/2	Mean 5.25 m	2	1	
Bajwa et al[32]	Retrospective descriptive case series	BSCR	Persistent vitritis, subretinal fluid	1/2	20 m	6	3	2.67
Bajwa et al[32]	Retrospective descriptive case series	BSCR	Vitritis+CME	1/2	24 m	8	4	
Bajwa et al[32]	Retrospective descriptive case series	BSCR	Vitritis+CME	1/2	At least 12 m	2	1	
Latronico et al[33]	Case report	VKH	Bilateral exudative retinal detachments and edema, vitritis, papillitis	1/2	6 times	2	1	1.27
Elhamaky et al[34]	Prospective study	VKH	Relapsing posterior uveitis in chronic recurrent VKH	16/29	Mean 24.75 ± 0.9 m	37	1.2	
Myung et al[31]	Retrospective chart review	VKH	Subretinal fluid	1/2	Mean 5.25 m	3	1.5	
Myung et al[31]	Retrospective chart review	Idiopathic	Vitritis, papillitis, and vasculitis, CME	1/1	Mean 5.25 m	2	2	1.5
Myung et al[31]	Retrospective chart review	Idiopathic	CME	1/1	Mean 5.25 m	1	1	

Table continued

Table I. ***(Continued).*** The number of injections for different etiologies and indications.

	Design	Etiology/ diagnosis	Indications	Number of patients/eyes	Follow-up (m)	Total injections (n)	Average injections (n)	Overall average (n)
Ahn et al[35]	Case report	Adult-onset Still's disease	Refractory uveitis and scleritis, refractory ocular inflammation	1/1	4 m	1	1	1
Wocker and Januschowski[36]	Case report	SO	CME	1/1	10 m	3	3	3
Palla et al[37]	Retrospective study design	Intermediate uveitis	CME, vitritis	15/20	Within 1 year period	20	1	1
Hasanreisoglu et al[19]	Case presentation.	TB	Persistent CME	1/1	10 m	1	1	1.03
Jain et al[21]	Retrospective review	TB	Multifocal serpiginoid choroiditis (MSC); progressive inflammation, or appearance of new lesions within 6 weeks of initiation of ATT	6/9	Mean 13.11 ± 6.05 m	9	1	
Agarwal et al[22]	Retrospective analysis	TB	Active uveitis with CME in 10 eyes, paradoxical worsening of MSC lesions in 2 eyes, to avoid systemic corticosteroids/corticosteroid intolerance in 3 eyes, 4 eyes active TB-related retinal vasculitis	17/19	Minimum of 3 m	19	1	
Fonollosa et al[20]	Case Report	TB	Multifocal serpiginoid choroiditis lesions progressed	1/1	At least 1 year	2	2	
Dutta Majumder et al[23]	Case Report	Syphilis + HIVpositive	Refractory CME	1/1	At least 9 m	2	2	3
Lautredou et al[24]	Case Report	Syphilis + HIV-positive	Refractory CME	1/1	15 m	4	4	

m: months; n: numbers; BD: Behcet's disease; VKH: Vogt-Koyanagi-Harada disease; SO: Sympathetic Ophthalmitis; BSCR: Birdshot Chorioretinopathy; TB: Tuberculosis; CME: Cystoid Macular Edema.

Efficacy

Indices of post-injection efficacy include reduced CMT, improved visual acuity, improvement in inflammation, and reduction in systemic therapy. Since the improvement of visual acuity is closely related to the resolution of macular edema[50], changes in visual acuity are not analyzed separately, but together with changes in CMT. It has been mentioned above that even if DEX-I is chosen for the same indication, there are differences in the number of injections required. Therefore, we further analyzed the treatment outcomes of macular edema and possible influencing factors.

Macular Edema Short-Term Outcomes (≤ 6 Months) *vs.* Long-Term utcomes (> 6 Months)

In uveitis, most sight loss is caused by macular edema[3,51]. Macular edema occurs in approximately 33% of uveitis, of which 44% results in visual acuity lower than 20/60[52]. Corticosteroid is a powerful anti-edema agent, widely used in local areas, such as subconjunctival, parabulbar, sub-tenon capsule or intravitreal[51]. An animal pharmacokinetic study[13] of ***Macaca fascicularis*** demonstrated sustained release of dexamethasone in the vitreous for 6 months and the peak concentrations occurred during the first two months[13]. Therefore, we chose the follow-up time ≤ 6 months as the short-term outcome and the follow-up time > 6 months as the long-term outcome of the treatment of macular edema. These results are derived from studies in the literature with only an indication of macular edema, having well-defined baseline characteristics, duration of follow-up, and treatment outcomes, excluding childhood uveitis, surgery-related, and unilateral injection bilateral impact research. The results are shown in Table II.

Three retrospective studies[53-55] with a follow-up period of 6 months showed that despite differences in disease course and etiology, CMT was < 300 μm at last follow-up after an average of one injection (one study[55] showed peak 291.24 ± 44.82 μm at 3 months, 309.73 ± 73.03 μm at 6 months) and visual acuity improved significantly at 1-3 months, maintaining until the last follow-up[53-55]. The results are consistent with a clinical trial[60] about vision-related functioning outcomes of DEX-I. In many retrospective studies[19,25,27,41,47,49,56-59] or case reports[24,36] with a follow-up of more than 6 months, the number of DEX implantation for macular edema was generally greater than one implant, and the time for re-injection was 3-6 months or 6 months later[19,24,25,27,36,41,47,49,56-59]. Although persistent, CME secondary to tuberculosis uveitis can achieve edema relief with only one injection, but other refractory or recurrent CME often required more injections. After multiple injections, CMT can still be reduced or completely relieved at 1-3 months, and VA will also improve. But there was a study[49] that showed several DEX implants reduced CMT but had no effect on VA. This may be because there was a correlation between the amount of VA change with a change in CMT and a change in cystoid space height over time[54]. Other studies[23,42,61-63] also showed that DEX-I can result in continuous and complete regression of uveitic cystoid macular edema[23,42,61-63]. A study[38] reported that the anatomical classification of uveitis does not affect the improvement of visual acuity after injection, but the visual change of intermediate uveitis is more significant[38]. In conclusion, DEX-I has an effective therapeutic outcome for macular edema caused by infectious or non-infectious uveitis.

Inflammatory Markers Change

Recurrent and chronic inflammation is another cause of irreversible damage to vision. Standardization of Uveitis Nomenclature guidelines[64] were followed for measuring anterior chamber cells, flare, and vitreous haze. Previous literature has shown that ocular inflammation usually decreases within 3 months after injection. A study by Kim et al[30] showed that the anterior chamber cells were 0.8 ± 0.8 before injection, 0.2 ± 0.3 at 1 months, 0.2 ± 0.4 at 6 months after injection[30]. According to Bratton et al[46], 17 of 22 insertions [12 eyes (77%)] showed improvement in intraocular inflammation after 1-3 months[46]. In improving vitreous opacity, Zeng et al[65] showed that at 1 month there was 81.48% improvement, while at 6 months it was 63.64%[65]. In Mathis et al's study[66], 81.4% of eyes had a vitreous haze score of 0 over time, and a significant improvement in 89.9% of cases. Berkenstock et al[67] also showed the proportion of eyes with vitreous cells > 0.5+ was 25% at 6 months and 21% at 12 months, whereas before injection it was 39% of eyes[67].

Systemic Therapy-Sparing Effect

Ozurdex can reduce systemic therapy, especially systemic corticosteroids and immunosuppressants. The results are shown in Table III. After the injection, the number of patients administrated by systemic therapy and dose of systemic corticosteroids were reduced, while there were cases with maintained unchanged situation[31,42,73]. The

Table II. Macular edema short-term outcomes (≤ 6 months) *vs.* long-term outcomes (> 6 months).

	Design	Follow-up (m)	Number of patients/eyes (n)	Total injections (n)	Average injections (n); re-injection	Time to re-injection	Course of disease (m)	Indications	Etiology/diagnosis	Baseline CMT (um)	Post-injection CMT (um)	Baseline BCVA	Post-injection BCVA
Rossetto et al[53]	Retrospectively	Mean 5	5/6	6	1			CME	IU associated with JIA, idiopathic IU	Mean 502.5	Improvement in all eyes, mean 261.3 at final	Mean 0.19	Mean 0.35 final VA, BCVA improved in all eyes of two or more lines
Bansal et al[54]	Prospective, interventional, nonrandomized study	Mean 6	27/30	30	1		17.14 ± 7.24 m	CME	IU, Idiopathic panuveitis, JIA associated uveitis, HLAB27 (+), BD, Sarcoidosis	Mean 524 ± 88.27	Peak 252.12±35.34 at 6 weeks, 289.07±73.39 at 24 weeks	Mean 0.62±0.23	Peak 0.23±0.17 LogMAR at 6 weeks, 0.33±0.31 LogMAR at 24 weeks
Fabiani et al[55]	Retrospectively	Mean 6	22/22	22	1		3.5 ± 2.5 yeas	CME	Idiopathic uveitis, BD, VKH	Mean 521.95 ±155.93	Peak 291.24 ± 44.82 at 3m, 309.73 ± 73.03 at 6 m	Snellen chart in decimal fractions 3.63 ± 1.93	6.29 ± 2.42 at 3m, 6.50±2.42 at 6 m
Tsang et al[56]	Retrospective chart review	Average 9	15/25	35	Mean 1.4; 1 implant: 18 eyes, 2 implants: 4 eyes, 3 implants: 3 eyes	6 Months		CME	BSCR, sarcoidosis, psoriatic arthritis and uveitis, multiple sclerosis, autoimmune retinopathy, andidiopathic intermediate or panuveitis	Mean 590	370 at 3 m, peak at 4 m	0.614 logMAR	Peak 0.35 logMAR at 3 months
Yap et al[57]	Retrospectively	Up to 10	4/6	7	Mean 1.17; 1 implant: 5 eyes, 2 implants: 1 eye			CME	BSCR, Idiopathic IU, Panuveitis	Mean 556	329 at 2 weeks	63 letters	70 letters at 2 weeks
Wocker and Janus chowski[36]	Case Report	10	1/1	3	3	Mean 3.5 months		CME	SO		CME resolution at last visit	0.8	0.63 at the final
Hasanreisoglu et al[19]	Case presentation	10	1/1	1	1			Persistent CME	TB	Persistent CME	Without CME	20/50	20/32
Kang et al[49]	Retrospectively	Mean 11.5 ± 6.9	37/52	110	Mean 2.1; 1 implant: 24 eyes, 2 implants: 15 eyes, 3 implants: 7 eyes, >3 implants: 6 eyes	6 Months		Refractory uveitic ME	Idiopathic uveitis, BD, JIA, VKH, AAU	Mean 507.5±121.7	A significant decrease in CMT 1 month after the first DEX	0.81±0.35 LogMAR	Significant VA improvement at both 1 and 2 months
Khurana et al[58]	Prospective interventional case series	Mean 12	10/10	20	Mean 2; 1 implant: 40%, 2 implants: 30%, 3 implants: 20%, 4 implants: 10%		Mean 8.4 m	CME along with quiescent uveitis	IU, Idiopathic, MFC, Granuloma Annulare, AS	Mean 438±157	The mean decreases 158±101 at 12 months; complete resolution of CME in 90% at 1 month and 70% at 3 months	Mean ETDRS BCVA was 53.8±19.8 letters	The mean increase in BCVA (±SD) was 16.5±12.0 letters at Month 12
Nobre-Cardoso et al[41]	Retrospectively	Mean 13.4 ± 5.9	31/41	58	Mean 1.4; 1 implant: 68.3%, 2 implants:24.4%, 3 implants: 4.9%, 4 implants: 2.4%	Mean of 7.1±2.9 months	Mean 5.5±3.1 m	CME	Idiopathic, Sarcoidosis, BD, VKH, Eales disease	Mean 461.1±158.2	Peak median 291 at 1 month, median 323 at 12 m	0.84±0.81 LogMAR	Peak median 0.40 LogMAR at 3 months, median 0.50 LogMAR at 12 months
Cao et al[47]	Retrospectively	Mean 14.5	27/27	>66	1 implant: 4 eyes, 2 implants: 7 eyes, ≥2 implants: 16 eyes	Mean interval of 4.6 months		Persistent uveitic ME	HLA-B27, Idiopathic uveitis, Pars planitis, BSCR, Sarcoidosis	Mean 478.7	Mean 278.9 at 1 month, all patients reached maximal resolution of CME 1 month	0.60 logMAR	0.41 logMAR significant improvement at 3 months
Lautredou et al[24]	Case Report	15	1/1	4	4	3 Months		Refractory CME	Syphilis+HIV-positive	CME	Complete resolution of CME	20/80	20/30
Fonollosa et al[25]	Retrospectively	Median 18	7/8	16	2			Refractory to or recurrent ME	HVS-1, *Treponema pallidum,* VZV, *Brucella melitensis*, *Borrelia burgdorferi*, Toxoplasma gondii, CMV	Mean 516	266.3	Median 20/160	Median 20/70
Ratra et al[59]	Retrospectively	Mean 19.2 ± 2.2	34/42	56	Mean 1.33; 1 implant: 31 eyes, 2 implants: 8 eyes, 3 implants: 3 eyes	The second mean 16.8±2.1 months, the third mean 12.9 ± 3.6 months	Mean 35.5 ± 12.7 m	Unresponsive, refractory, chronic ME	IU, presumed tubercular IU, Serpiginous choroiditis, Healed toxoplasma retinochoroiditis, Eale's disease	Mean 472.2±35	Peak 200 at 3 m, 274.7±60.6 at the final	0.48±0.06 logMAR	0.34±0.1 logMAR during the final
Yalcinbayir et al[27]	Retrospective and cross-sectional study	Mean 24.35 ± 9.86	20/27	32	Mean 1.18 ± 0.32; 5 eyes received a second injection	Mean 16.8±3.54 months		CME	BD	Mean 406 ± 190	Peak 201±34 at 2 m, 243±101 at 6 m	0.85±0.72 logMAR	Peak mean 0.36±0.43 logMAR within 1.81±1.41 months, 0.45± .52 logMAR at 6 m

AAU: Acute anterior uveitis; MFC: Multifocal Choroiditis; HVS-1: Herpes Virus simplex-1; VZV: Varicella-Zoster virus; CMV: Cytomegalovirus; m: months; n: numbers; BCVA: best-corrected visual acuity; CMT: Central Macular Thickness; ME: Macular Edema; CME: Cystoid Macular Edema; IU: Intermediate Uveitis; JIA: Juvenile Idiopathic Arthritis; BD: Bechet's disease; VKH: Vogt-Koyanagi-Harada disease; BSCR: Birdshot Chorioretinopathy; SO: Sympathetic Ophthalmitis; TB: Tuberculosis; AS: Ankylosing Spondylitis.

Table III. Systemic therapy-sparing effect.

	Systemic corticosteroid [patients (n, %), mean dosage]		Immunosuppressive drug therapy [patients (n, %), mean dosage]	
	Pre-injection	Post-injection	Pre-injection	Post-injection
Zeng et al[65]	16.71±10.25 mg/day	11.81±9.81 mg/day at 3 months and 12.2±11.45 mg/day at 6 months	——	——
Mathis et al[66]	70 mg/day	5 mg/day	——	——
McCartney et al[39]	(8, 47%)	(7, 41.18%) reduce their prednisolone dose to below 7.5 mg/day. Three were able to cease	(7, 41%)	——
Kim et al[30]	(8, 40%)	(6, 30%) discontinued	(12, 60%)	(2, 10%) were able to achieve dose reduction of immunosuppressant.
Hasanreisoğlu et al[68]	(16, 36.36%), median dose of 16 mg	(8, 18.2%)	(20, 45.45%)	(16, 36.36%)
Bajwa et al[32]	——	——	Cyclosporin A 200 mg/d	Mycophenolate mofetil 2,000 mg/d + cyclosporin A 200 mg/d
Agarwal et al[22]	(13, 76.47%), 1 mg/kg	(8, 47.05%), <10 mg/day, then stopped within 8 weeks	——	——
Tsang et al[56]	——	——	(5, 33.33%)	Remained on their systemic therapy throughout the course of follow-up
Breitbach et al[61]	(49, 100%), 6.2±3.3 mg	(49, 100%)	(45, 92%)	(45, 92%)
Coskun et al[29]	(11, 91.67%), 21.45 mg daily	All patients discontinued within 1 month	100%	Continued in all
Miserocchi et al[69]	(7, 58.33%), 22.14 mg/day	(7, 58.33%), 14.64 mg/day final	(8, 66.67%)	(8, 66.67%) final
Nobre-Cardoso et al[41]	(21, 67.7%)	Reduced or halted	(8, 25.8%)	Maintained unchanged
Bernard et al[63]	——	Reduced	——	——
Ryder et al[42]	(6, 60%)	Continued during the follow-up period	(1, 10%)	Continued during the follow-up period.
Lam et al[70]	(10, 43.5%) eyes	(4, 17.4%) eyes	Mycophenolate mofetil (6, 26.1 %), methotrexate (7, 30.4%) eyes	Mycophenolate mofetil (11, 47.8%), methotrexate (4, 17.4%) eyes
Habot-Wilner et al[71]	——	——	(1, 14.29%) mycophenolate mofetil 2 g/day	(1, 14.29%) mycophenolate mofetil 1.5 g/day.
Myung et al[31]	60 mg	Off oral steroids (one case), not changed (one case)	——	——
Li et al[72]	(7, 100%), 26.43 mg/d	(4, 57.14%), 8.13 mg/d	(5, 71.43%)	(3, 42.86%), all usage decreased
Pelegrín et al[44]	(13, 40.3%)	Dose reduction prednisone was tapered in all cases at 1 month	(9, 28.1%)	——
Adan et al[73]	(6, 46.15%)	Not changed	(3, 3.08%)	Not changed

Table continued

median dose of corticosteroids after the reduction was 9.0 ± 10.68 mg/day. There was also a dose-reducing effect on immunosuppressants, but it was weaker than the effect on corticosteroids, and a

Table III. ***(Continued).*** Systemic therapy-sparing effect.

	Systemic corticosteroid [patients (n, %), mean dosage]		Immunosuppressive drug therapy [patients (n, %), mean dosage]	
	Pre-injection	**Post-injection**	**Pre-injection**	**Post-injection**
Adan et al[73]	(6, 46.15%)	Not changed	(3, 3.08%)	Not changed
Ratra et al[59]	(41, 97.6%) eyes	(24, 57.2%) eyes	(28, 69%) eyes	(21, 50%,) eyes
Taylor et al[74]	(6, 54.55%), 17.9±3.4 mg	(6, 54.55%), 2.1±1.2 mg	——	——
Habot-Wilner et al[75]	0	0	Mycophenolate mofetil 2 g/day	Mycophenolate mofetil could be further reduced to 1 g/day
Berkenstock et al[67]	(6, 30%), a median dose of 17.5 mg daily	(2, 10%) stopped; (4, 20%) tapered to 7.5 mg daily or less by 12 months	(17, 85%)	(15, 75%)
Fabiani et al[55]	(19, 86.4%), 20.00±7.39 mg/day	15.25±9.01 at 1-month, 9.0±10.68 at 6-month	(13, 59.1%) at 1 month	——
Frere et al[76]	(5, 36%)	(4, 28.6%) early and late after DEX-I	(6, 43%) just before implant	(5, 36%) early after DEX-I, and (9, 64.2%) late after DEX-I

n: numbers; DEX-I: Dexamethasone Intravitreal implant.

few patients required additional immunosuppressants[32,70].

Special Research

Treating pediatric uveitis (age < 16 years or JIA-associated uveitis)

A single-center retrospective cohort study[77] in Switzerland showed that 317 (11.1%) of 2,846 patients with uveitis, who presented to the clinic, were younger than 16 years old between 2000 and 2019. At the onset of uveitis, the median age was 8.9 years and non-anterior uveitis was 54.9%[77].

Treatment of uveitis in children is limited, mainly due to side effects of drugs. Intravitreal dexamethasone implants effectively avoid this situation. The most common indication for Ozurdex in children is macular edema, followed by vitritis. A study[40] showed that patients with Juvenile Idiopathic Arthritis (JIA)-associated uveitis, mean age 17.5 ± 6.7 years, received an average of 2.1 injections per eye during a mean follow-up of 15.6 ± 12.2 months, which results in the mean CMT decreased from 437.6 ± 96.2 μm to 342.4 ± 79.3 μm and after 1 months, BCVA significantly increased to 39.6 ± 11 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/40)[40]. However, a study by Lei and Lam[78] showed an average of 3 injections for macular edema[78]. A study by Tomkins-Netzer et al[79] reported that 17 CME (77.3%) and 5 vitritis (22.7%) required an average of 1.59 injections[79]. Intraocular inflammation (anterior chamber cells and vitreous haze) was improved at 1-3 months after first injection, then remained stable[40,46,74,80,81]. The mean BCVA had significant improvement with lower CMT and improved intraocular inflammation. For systemic therapy sparing effect, the majority of patients treated with systemic therapy were able to stop or reduce their treatment[74,79]. A study[59] comparing DEX implantations in adults and children showed no significant difference in results. Overall, 24.7% (19/77) of the affected eyes had elevated IOP (IOP > 21 mmHg or experienced IOP elevation > 10 mmHg) after the injection in children. A study about JIA-associated uveitis by Pichi et al[40] showed that the mean IOP was increased to 25 mmHg after the first injection at 1 month[40]. In addition, Taylor et al[74] and Tomkins-Netzer et al[79] reported a series of post-injection elevated IOP requiring antiglaucoma surgery[74,79]. Cataract progression or formation accounted for about 26.6% (18/74).

Utilizing in Surgery

Uveitis is usually accompanied by cataracts. For the treatment of cataract, phacoemulsification combined with intraocular lens implantation is the preferred therapy. Due to the specific natu-

re of the disease, cataract surgery is more likely to lead to inflammatory recurrence and macular edema. A randomized, parallel design, and clinical trial[82] about preventing post-operative CME has compared a study group that received the intravitreal dexamethasone implant during cataract surgery with a control group that started oral corticosteroids two days prior to surgery. The results showed that in one patient of the study group and in two patients of the control group CME occurred. So, DEX-I is a good alternative in preventing post-operative CME in intermediate or posterior uveitis and cataract[82]. Another prospective study[83] has also compared a phaco+implant group (intraoperative intravitreal dexamethasone implant) with a phaco+oral steroids group (postoperatively, oral steroids were given without the implant) and found that CME occurred in 1 eye on both groups[83]. Therefore, in patients with uveitis and cataract, a single intra-operative DEX-I is an effective alternative to oral steroids after phacoemulsification. Both groups did not show significant differences in terms of BCVA, central retinal thickness (CRT), IOP. In another prospective study[84], about preventing post-operative inflammation recurrence by DEX-I, reported that in the study group (receiving DEX-I), the inflammation settled very early compared to the control group (standard of care)[84]. Therefore, it is a good alternative for the prevention of post-operative inflammation and CME in uveitis with cataract[72,82-85]. It has also been shown[86] that DEX-I is effective in the treatment of macular edema after intraocular surgery. In addition, DEX-I can be used as perioperative anti-inflammatory medication. Two retrospective studies[65,87] of real-world reported patients received DEX-I one month before surgery and then, uveitis remained quiet during follow-up. For uveitis with vitrectomized eyes and non-vitrectomized eyes, Pelegrín et al[44] and Adan et al[73] showed the same efficacy, and there was no significant difference. A study by Pang et al[88] reported that combined vitrectomy and intravitreal dexamethasone implant can maintain edema-free status for 12.91 ± 7.85 months following noninfectious posterior uveitis[88].

Bilateral Influence

An interesting observation is that in patients with bilateral uveitis with unilateral injection, the fellow eye also showed improvement in macular edema and in inflammation leading to improved visual acuity. Habot-Wilner et al[75] reported several patients with bilateral macular edema and vitritis. Ozurdex is injected in the right eye; after 2 months of injections, both eyes were free of vitritis. Macular edema in the right eye completely resolved one week later and improved in the left as well one week later, then in the last 24 months, no macular edema was detected in both eyes. The right eye's vision improved to 20/27 and the left eye to 20/25[75]. Tomkins-Netzer et al[43], Zeng et al[65] and Santos et al[89] also found that the other eye with bilateral non-infectious uveitis also responded, with a decrease in CMT and an improvement in BCVA after transplantation in the first eye.

Safety

At least 1,885 eyes coming from 75 articles were treated with DEX-I. 1,511 eyes coming from 58 articles were recorded with intraocular pressure changes and then 310 eyes (20.52%) experienced increased intraocular pressure. In addition, 1,184 eyes coming from 42 articles were recorded with lens status changes, for example from Lowder et al[90] and Kim et al[91], and 178 eyes (15.51%) had cataract formation or progression. This is similar to that reported in the HURON Study[90] and Fassbender Adeniran et al[92]. Most of the high intraocular pressure only needs to be treated with hypotensive drugs, and a few needs anti-glaucoma surgery, or even surgery to remove the implant[93]. Cataracts are associated with DEX exposure and follow-up time[94]. In addition to elevated intraocular pressure and cataracts, other side effects included: implant dislocation into the anterior chamber (11 cases), hypotony (10 cases), vitreous hemorrhage (10 cases), pain and redness at the injection site (5 cases), retinal detachment (3 cases), endophthalmitis (1 case), subconjunctival hemorrhage (1 case), Intra-lenticular Implantation (1 case). Implant migration into the anterior chamber occurs most often in the aphakic eye and pseudophakic eye[43,44,46,73,86,95]. Additionally, Olson et al[96] reported a case of reactivation of latent intraocular infections and Kucukevcilioglu et al[97] reported an acute retinal necrosis following intravitreal dexamethasone implant. Kim and Lee[98] also reported a cytomegalovirus retinitis after the placement of an intravitreal dexamethasone implant in immunocompetent patients with no history of risk factors or immunosuppression. A study[92] reported some rare adverse events during the expansion use of DEX-I such as: fracture or split of the implant, implant trapped in

the macula, vitreomacular traction. It should be noted that for patients with bilateral uveitis, considering whether the drug is effective and safe after injection, the interval time between eyes is generally one week[22,26,29,42,65,72]. However, a retrospective study by Kapoor and Colchao[99] showed that consecutive same-day bilateral Ozurdex is secure and properly tolerated[99]. Overall, all patients undergoing Ozurdex implantation require special attention and frequent follow-up.

Is Intravitreal Dexamethasone Implants as Effective as Monotherapy or Only as an Adjunct to Systemic Therapy?

With the DEX-I widespread used, are uveitis specialists aware of whether it can replace oral corticosteroids as a monotherapy, or only as an adjunct to systemic therapy? There are currently no relevant clinical studies to explore this issue. A long-term retrospective study[100] with a mean follow-up of 56.8 months over 82 months, reported that 79 eyes of 63 patients received a total of 134 injections, with a mean injection of 1.6 ± 1.1, pre-injection systemic corticosteroid therapy accounting for 90% (57/63), of which ≥ 10 mg/day accounting for 49% (31/63), immunosuppressant treatment accounting for 63.4% (40/63), and then the probability of corticosteroid-sparing or immunosuppressant-sparing effect after injection was 87.7% (50/ 57) at 12 months. Corticosteroid dose reduction was achieved by 100% (31/31) at 12 months[100]. Another retrospective study[26], with a mean follow-up of 18.4 months, reported DEX-I as a monotherapy treatment for tuberculous uveitis, the mean number of injections was not specified in the text, but vitreous opacity, CMT, and visual acuity significantly improved at 3 months and no recurrence was registered within one year[26]. Both studies[26,100] evaluated long-term outcomes, with the former showing a reduction in the systemic therapy after DEX-I injections, but dexamethasone intravitreal implant's effectiveness was not affected, and the latter showing that even without the systemic therapy, after injections, dexamethasone intravitreal implant's treatment outcome is still effective.-The difference between the studies lies in the etiology, indication and in the disease's course. The author believes that whether DEX-I, as an intravitreal short-acting sustained-release agent, is used as a monotherapy to control these chronic diseases related to systemic immune disorders needs to be comprehensively considered. It may be related to the following aspects: the etiology and course, the treatment of systemic diseases, whether multiple injections can be tolerated, the complications after multiple injections, economic situation, etc. In addition, if long-acting sustained-release intravitreal corticosteroids (e.g., fluocinolone acetonide[101]) can supplement anti-inflammatory therapy of DEX-I, systemic therapy and side effects such as femoral head necrosis caused by oral glucocorticoid-induced abnormal hyperplasia of chondrocytes can be avoided[102]. From the current research, it has been widely recognized as an adjuvant for systemic therapy, and its effectiveness as a monotherapy needs further research. Future research can develop in the direction of intravitreal injection of corticosteroids instead of the systemic administration of corticosteroids, which will greatly improve the quality of life of patients.

Conclusions

Ozurdex has been used in uveitis for more than 10 years. It has shown a good effect on improving macular edema, inflammation and visual acuity; therefore, it has become an alternative therapy for uveitis. The effective time is only 3 to 6 months, making repeated injections necessary, so we need strict follow-up and observation of post-injection complications. Whether it is used as a monotherapy or only as an adjunct to systemic therapy further research is required. At the same time, more indications also need to be studied by uveitis experts.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contributions

Shun Zeng substantially contributed to the conception, design and drafting of the work and the acquisition, analysis and interpretation of the data of the work. Xiaoli Liu revised it critically for important intellectual content and approved the final version of the article to be published.

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All data generated or analyzed during this study are included in this published article.

References

1) Krishna U, Ajanaku D, Denniston AK, Gkika T. Uveitis: a sight-threatening disease which can impact all systems. Postgrad Med J 2017; 93: 766-773.
2) De Smet MD, Taylor SR, Bodaghi B, Miserocchi E, Murray PI, Pleyer U, Zierhut M, Barisani-Asenbauer T, LeHoang P, Lightman S. Understanding uveitis: the impact of research on visual outcomes. Prog Retin Eye Res 2011; 30: 452-470.
3) Durrani OM, Meads CA, Murray PI. Uveitis: a potentially blinding disease. Ophthalmologica 2004; 218: 223-236.
4) Hsu YR, Huang JC, Tao Y, Kaburaki T, Lee CS, Lin TC, Hsu CC, Chiou SH, Hwang DK. Noninfectious uveitis in the Asia-Pacific region. Eye (Lond) 2019; 33: 66-77.
5) Hao T, Yang LI, Li B, Chen X, Li D, Liu X. Epidemiology of 2000 Chinese uveitis patients from Northeast China. Br J Ophthalmol 2021; 105: 317-321.
6) Gonzalez MM, Solano MM, Porco TC, Oldenburg CE, Acharya NR, Lin SC, Chan MF. Epidemiology of uveitis in a US population-based study. J Ophthalmic Inflamm Infect 2018; 8: 6.
7) Miserocchi E, Fogliato G, Modorati G, Bandello F. Review on the worldwide epidemiology of uveitis. Eur J Ophthalmol 2013; 23: 705-717.
8) Gao F, Zhao C, Cheng G, Pei M, Liu X, Wang M, Jia S, Zhang M. Clinical Patterns of Uveitis in a Tertiary Center in North China. Ocul Immunol Inflamm 2017; 25: S1-S7.
9) Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol 1996; 80: 332-336.
10) Koronis S, Stavrakas P, Balidis M, Kozeis N, Tranos PG. Update in treatment of uveitic macular edema. Drug Des Devel Ther 2019; 13: 667-680.
11) Ferreira LB, Farrall AL, Furtado JM, Smith JR. Treatment of noninfectious uveitis. Arq Bras Oftalmol 2021; 84: 610-621.
12) Whitcup SM, Robinson MR. Development of a dexamethasone intravitreal implant for the treatment of noninfectious posterior segment uveitis. Ann N Y Acad Sci 2015; 1358: 1-12.
13) Chang-Lin JE, Attar M, Acheampong AA, Robinson MR, Whitcup SM, Kuppermann BD, Welty D. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. Invest Ophthalmol Vis Sci 2011; 52: 80-86.
14) Kishore K, Bhat PV, Venkatesh P, Canizela CC. Dexamethasone Intravitreal Implant for the Treatment of Macular Edema and Uveitis: A Comprehensive Narrative Review. Clin Ophthalmol 2022; 16: 1019-1045.
15) Massa H, Georgoudis P, Panos GD. Dexamethasone intravitreal implant (OZURDEX(®)) for macular edema secondary to noninfectious uveitis: a review of the literature. Ther Deliv 2019; 10: 343-351.
16) Omer Karti AOS. Intravitreal Dexamethasone Implant in the Treatment of NonInfectious Uveitic Macular Edema. Med Hypothesis Discov Innov Ophthalmol 2018; 7: 169-175.
17) Yu C, MacDougall D. Intravitreal Dexamethasone Implants for Non-infectious Uveitis: A Review of Clinical Effectiveness, Cost-effectiveness, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health 2020.
18) Burkholder BM, Moradi A, Thorne JE, Dunn JP. The Dexamethasone Intravitreal Implant for Noninfectious Uveitis: Practice Patterns Among Uveitis Specialists. Ocul Immunol Inflamm 2015; 23: 444-453.
19) Hasanreisoglu M, Gulpinar Ikiz G, Aktas Z, Ozdek S. Intravitreal dexamethasone implant as an option for anti-inflammatory therapy of tuberculosis uveitis. Int Ophthalmol 2019; 39: 485-490.
20) Fonollosa A, Valsero S, Artaraz J, Ruiz-Arruza I. Dexamethasone intravitreal implants in the management of tubercular multifocal serpiginoid choroiditis. J Ophthalmic Inflamm Infect 2016; 6: 31.
21) Jain L, Panda KG, Basu S. Clinical Outcomes of Adjunctive Sustained-Release Intravitreal Dexamethasone Implants in Tuberculosis-Associated Multifocal Serpigenoid Choroiditis. Ocul Immunol Inflamm 2018; 26: 877-883.
22) Agarwal A, Handa S, Aggarwal K, Sharma M, Singh R, Sharma A, Agrawal R, Sharma K, Gupta V. The Role of Dexamethasone Implant in the Management of Tubercular Uveitis. Ocul Immunol Inflamm 2018; 26: 884-892.
23) Dutta Majumder P, Mayilvakanam L, Palker AH, Sridharan S, Biswas J. Intravitreal sustained-release dexamethasone implant for the treatment of persistent cystoid macular edema in ocular syphilis. Indian J Ophthalmol 2019; 67: 1487-1490.
24) Lautredou CC, Hardin JS, Chancellor JR, Uwaydat SH, Ellabban AA, Sallam AB. Repeat Intravi-

treal Dexamethasone Implant for Refractory Cystoid Macular Edema in Syphilitic Uveitis. Case Rep Ophthalmol Med 2018; 2018: 7419823.

25) Fonollosa A, Llorenc V, Artaraz J, Jimenez B, Ruiz-Arruza I, Agirrebengoa K, Cordero-Coma M, Costales-Mier F, Adan A. Safety and efficacy of intravitreal dexamethasone implants in the management of macular edema secondary to infectious uveitis. Retina 2016; 36: 1778-1785.
26) Baharani A, Reddy P RR, Patil PM. The Efficacy and Safety of Intravitreal Dexamethasone Implant as Anti-inflammatory Monotherapy in the Management of Tuberculosis-associated Intermediate Uveitis. Ocul Immunol Inflamm 2021: 1-9.
27) Yalcinbayir O, Caliskan E, Ucan Gunduz G, Gelisken O, Kaderli B, Yucel AA. Efficacy of Dexamethasone Implants in Uveitic Macular Edema in Cases with Behcet Disease. Ophthalmologica 2019; 241: 190-194.
28) Fabiani C, Emmi G, Lopalco G, Vannozzi L, Bacherini D, Guerriero S, Franceschini R, Frediani B, Lannone F, Tosi GM, Rigante D, Cantarini L. Intravitreal Dexamethasone implant as an Adjunct Weapon for Severe and Refractory Uveitis in Behcet's Disease. Isr Med Assoc J 2017; 19: 415-419.
29) Coskun E, Celemler P, Kimyon G, Oner V, Kisacik B, Erbagci I, Onat AM. Intravitreal Dexamethasone Implant for Treatment of Refractory Behcet Posterior Uveitis: One-year Follow-up Results. Ocul Immunol Inflamm 2015; 23: 437-443.
30) Kim M, Kim SA, Park W, Kim RY, Park YH. Intravitreal Dexamethasone Implant for Treatment of Sarcoidosis-Related Uveitis. Adv Ther 2019; 36: 2137-2146.
31) Myung JS, Aaker GD, Kiss S. Treatment of noninfectious posterior uveitis with dexamethasone intravitreal implant. Clin Ophthalmol 2010; 4: 1423-1426.
32) Bajwa A, Peck T, Reddy AK, Netland PA, Shildkrot Y. Dexamethasone implantation in birdshot chorioretinopathy - long-term outcome. Int Med Case Rep J 2018; 11: 349-358.
33) Latronico ME, Rigante D, Caso F, Cantarini L, Costa L, Nieves-Martin L, Traversi C, Franceschini R. Bilateral dexamethasone intravitreal implant in a young patient with Vogt-Koyanagi-Harada disease and refractory uveitis. Clin Rheumatol 2015; 34: 1145-1148.
34) Elhamaky TR. Long-term efficacy of dexamethasone intravitreal implant in the treatment of Vogt-Koyanagi-Harada disease relapsing posterior uveitis. Indian J Ophthalmol 2022; 70: 2465-2470.
35) Ahn SJ, Hwang SJ, Lee BR. Intravitreal dexamethasone implants for the treatment of refractory scleritis combined with uveitis in adult-onset Still's disease: a case report. BMC Ophthalmol 2016; 16: 196.
36) Wocker L, Januschowski K. [Steroid implant in treatment of sympathetic ophthalmia: Intravitreal implant of dexamethasone in cystoid macular edema in the context of sympathetic ophthalmia]. Ophthalmologe 2019; 116: 380-383.
37) Palla S, Biswas J, Nagesha CK. Efficacy of Ozurdex implant in treatment of noninfectious intermediate uveitis. Indian J Ophthalmol 2015; 63: 767-770.
38) Han JY, Lee DH, Kim JD, Choi EY, Kim M. Therapeutic Efficacy of Intravitreal Dexamethasone Implant in Korean Patients with Non-infectious Uveitis. J Kor Ophthalmol Soc 2021; 62: 798-805.
39) McCartney M, McCluskey P, Zagora S. Intravitreal dexamethasone implants for non-infectious uveitis. Clin Exp Ophthalmol 2019; 47: 1156-1163.
40) Pichi F, Nucci P, Baynes K, Lowder CY, Srivastava SK. Sustained-release dexamethasone intravitreal implant in juvenile idiopathic arthritis-related uveitis. Int Ophthalmol 2017; 37: 221-228.
41) Nobre-Cardoso J, Champion E, Darugar A, Fel A, Lehoang P, Bodaghi B. Treatment of Non-infectious Uveitic Macular Edema with the Intravitreal Dexamethasone Implant. Ocul Immunol Inflamm 2017; 25: 447-454.
42) Ryder SJ, Iannetta D, Bhaleeya SD, Kiss S. Efficacy and tolerability of bilateral sustained-release dexamethasone intravitreal implants for the treatment of noninfectious posterior uveitis and macular edema secondary to retinal vein occlusion. Clin Ophthalmol 2015; 9: 1109-1116.
43) Tomkins-Netzer O, Taylor SR, Bar A, Lula A, Yaganti S, Talat L, Lightman S. Treatment with repeat dexamethasone implants results in long-term disease control in eyes with noninfectious uveitis. Ophthalmology 2014; 121: 1649-1654.
44) Pelegrín L, De La Maza MS, Molins B, Ríos J, Adán A. Long-term evaluation of dexamethasone intravitreal implant in vitrectomized and non-vitrectomized eyes with macular edema secondary to non-infectious uveitis. Eye (Lond) 2015; 29: 943-950.
45) Sella R, Oray M, Friling R, Umar L, Tugal-Tutkun I, Kramer M. Dexamethasone intravitreal implant (Ozurdex(R)) for pediatric uveitis. Graefes Arch Clin Exp Ophthalmol 2015; 253: 1777-1782.
46) Bratton ML, He YG, Weakley DR. Dexamethasone intravitreal implant (Ozurdex) for the treatment of pediatric uveitis. J AAPOS 2014; 18: 110-113.
47) Cao JH, Mulvahill M, Zhang L, Joondeph BC, Dacey MS. Dexamethasone intravitreal implant in the treatment of persistent uveitic macular edema in the absence of active inflammation. Ophthalmology 2014; 121: 1871-1876.
48) Bodaghi B, Brézin AP, Weber M, Delcourt C, Kodjikian L, Provost A, Velard MÈ, Barnier-Ripet D, Pinchinat S, Dupont-Benjamin L. Real-Life Efficacy, Safety, and Use of Dexamethasone Intravitreal Implant in Posterior Segment Inflammation Due to Non-infectious Uveitis (LOUVRE 2 Study). Ophthalmol Ther 2022; 11: 1775-1792.
49) Kang EY, Garg SJ, Chen HF, Wu WC, Chen LY, Chou HD, Liu L, Chen KJ, Hwang YS. Intravitreal Dexamethasone Implants for Refractory Macular Edema in Eyes with Noninfectious Uveitis. J Clin Med 2021; 10: 3762.

50) Nussenblatt RB, Kaufman SC, Palestine AG, Davis MD, Ferris FL. Macular Thickening and Visual Acuity. Ophthalmology 1987; 94: 1134-1139.

51) Fardeau C, Champion E, Massamba N, LeHoang P. Uveitic macular edema. Eye (Lond) 2016; 30: 1277-1292.

52) Lardenoye CW, Van Kooij B, Rothova A. Impact of macular edema on visual acuity in uveitis. Ophthalmology 2006; 113: 1446-1449.

53) Rossetto JD, Nascimento H, Fernandes DD, Belfort R Jr, Muccioli C. Treatment of cystoid macular edema secondary to chronic non-infectious intermediate uveitis with an intraocular dexamethasone implant. Arq Bras Oftalmol 2015; 78: 190-193.

54) Bansal P, Agarwal A, Gupta V, Singh R, Gupta A. Spectral domain optical coherence tomography changes following intravitreal dexamethasone implant, Ozurdex® in patients with uveitic cystoid macular edema. Indian J Ophthalmol 2015; 63: 416-422.

55) Fabiani C, Vitale A, Emmi G, Lopalco G, Vannozzi L, Bacherini D, Guerriero S, Favale RA, Fusco F, Franceschini R, Frediani B, Iannone F, Galeazzi M, Tosi GM, Cantarini L. Systemic Steroid Sparing Effect of Intravitreal Dexamethasone Implant in Chronic Noninfectious Uveitic Macular Edema. J Ocul Pharmacol Ther 2017; 33: 549-555.

56) Tsang AC, Virgili G, Abtahi M, Gottlieb CC. Intravitreal Dexamethasone Implant for the Treatment of Macular Edema in Chronic Non-infectious Uveitis. Ocul Immunol Inflamm 2017; 25: 685-692.

57) Yap YC, Papathomas T, Kamal A. Results of intravitreal dexamethasone implant 0.7 mg (Ozurdex®) in non-infectious posterior uveitis. Int J Ophthalmol 2015; 8: 835-838.

58) Khurana RN, Bansal AS, Chang LK, Palmer JD, Wu C, Wieland MR. Prospective Evaluation of a Sustained-Release Dexamethasone Intravitreal Implant for Cystoid Macular Edema in Quiescent Uveitis. Retina 2017; 37: 1692-1699.

59) Ratra D, Barh A, Banerjee M, Ratra V, Biswas J. Safety and Efficacy of Intravitreal Dexamethasone Implant for Refractory Uveitic Macular Edema in Adults and Children. Ocul Immunol Inflamm 2018; 26: 1034-1040.

60) Lightman S, Belfort R Jr, Naik RK, Lowder C, Foster CS, Rentz AM, Cui H, Whitcup SM, Kowalski JW, Revicki DA. Vision-related functioning outcomes of dexamethasone intravitreal implant in noninfectious intermediate or posterior uveitis. Invest Ophthalmol Vis Sci 2013; 54: 4864-4870.

61) Breitbach M, Rack D, Dietzel M, Heinz C, Heiligenhaus A. [Efficacy of a Dexamethasone Implant for the Treatment of Refractory Cystoid Macular Oedema in Non-Infectious Uveitis]. Klin Monbl Augenheilkd 2016; 233: 601-605.

62) Teja S, Sawatzky L, Wiens T, Maberley D, Ma P. Ozurdex for refractory macular edema secondary to diabetes, vein occlusion, uveitis and pseudophakia. Can J Ophthalmol 2019; 54: 540-547.

63) Bernard Y, Bonnin N, Farguette F, Chiambaretta F. [Tolerability and short-term efficacy of the Ozurdex® dexamethasone intravitreal implant for treatment of uveitic cystoid macular edema: A retrospective study of 52 injections performed at the Clermont-Ferrand teaching hospital]. J Fr Ophtalmol 2016; 39: 1-4.

64) Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature Working G. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005; 140: 509-516.

65) Zeng S, Yang L, Bai F, Liu T, Liu X. Intravitreal dexamethasone implant for noninfectious uveitis in Chinese patients. Int Ophthalmol 2022; 42: 2063-2069.

66) Mathis T, Cerquaglia A, Weber M, Guillarme-Sallit R, Malcles A, Voirin N, Servant M, Sudhalkar A, Bilgic A, Denis P, Seve P, Bodaghi B, Kodjikian L. Real life study in Uveitis treated with Dexamethasone implant. Retina 2021; 41: 620-629.

67) Berkenstock MK, Mir TA, Khan IR, Burkholder BM, Chaon BC, Shifera AS, Thorne JE. Effectiveness of the Dexamethasone Implant in Lieu of Oral Corticosteroids in Intermediate and Posterior Uveitis Requiring Immunosuppression. Ocul Immunol Inflamm 2022; 30: 741-749.

68) Hasanreisoğlu M, Özdemir HB, Özkan K, Yüksel M, Aktaş Z, Atalay HT, Özdek Ş, Gürelik G. Intravitreal Dexamethasone Implant in the Treatment of Non-infectious Uveitis. Turk J Ophthalmol 2019; 49: 250-257.

69) Miserocchi E, Modorati G, Pastore MR, Bandello F. Dexamethasone intravitreal implant: an effective adjunctive treatment for recalcitrant noninfectious uveitis. Ophthalmologica 2012; 228: 229-233.

70) Lam WC, Albiani DA, Yoganathan P, Chen JC, Kherani A, Maberley DA, Oliver A, Rabinovitch T, Sheidow TG, Tourville E, Wittenberg LA, Sigouin C, Baptiste DC. Real-world assessment of intravitreal dexamethasone implant (0.7 mg) in patients with macular edema: the CHROME study. Clin Ophthalmol 2015; 9: 1255-1268.

71) Habot-Wilner Z, Sorkin N, Goldenberg D, Loewenstein A, Goldstein M. Long-term outcome of an intravitreal dexamethasone implant for the treatment of noninfectious uveitic macular edema. Ophthalmologica 2014; 232: 77-82.

72) Li YT, Cui XX, Yang XT, Li B, Ren XJ, Li XR, Zhang XM. Utilizing dexamethasone intravitreal implant to control postoperative inflammation in refractory uveitis undergoing cataract surgery. Int J Ophthalmol 2021; 14: 317-322.

73) Adan A, Pelegrin L, Rey A, Llorenc V, Mesquida M, Molins B, Rios J, Keller J. Dexamethasone intravitreal implant for treatment of uveitic persistent cystoid macular edema in vitrectomized patients. Retina 2013; 33: 1435-1440.

74) Taylor SRJ, Tomkins-Netzer O, Joshi L, Morarji J, McLoone E, Lightman S. Dexamethasone Implant

in Pediatric Uveitis. Ophthalmology 2012; 119: 2412-2412.e2.

75) Habot-Wilner Z, Sorkin N, Goldenberg D, Goldstein M. Bilateral effect of unilateral dexamethasone intravitreal implant in a case of noninfectious uveitic macular edema and vitritis. Retin Cases Brief Rep 2015; 9: 151-153.

76) Frere A, Caspers L, Makhoul D, Judice L, Postelmans L, Janssens X, Lefebvre P, Melot C, Willermain F. Single Dexamethasone Intravitreal Implant in the Treatment of Noninfectious Uveitis. J Ocul Pharmacol Ther 2017; 33: 290-297.

77) Hoogewoud F, Cohen J, Rossi D, Koryllou A, Guex-Crosier C, Ezziat S, Hofer M, Guex-Crosier Y. Epidemiology of Childhood Uveitis in a Tertiary Care Center: A 20-Year Study. Klin Monbl Augenheilkd 2021; 238: 469-473.

78) Lei S, Lam WC. Efficacy and safety of dexamethasone intravitreal implant for refractory macular edema in children. Can J Ophthalmol 2015; 50: 236-241.

79) Tomkins-Netzer O, Talat L, Seguin-Greenstein S, Bar A, Lightman S. Outcome of Treating Pediatric Uveitis With Dexamethasone Implants. Am J Ophthalmol 2016; 161: 110-115.e1-2.

80) Winterhalter S, Behrens UD, Salchow D, Joussen AM, Pleyer U. Dexamethasone implants in paediatric patients with noninfectious intermediate or posterior uveitis: first prospective exploratory case series. BMC Ophthalmol 2017; 17: 252.

81) Iarossi G, Coppè AM, Catena G, Petroni S, Montes M, Buzzonetti L. Dexamethasone Intravitreal Implant (Ozurdex) in Paediatric Patients with Non-infectious Intermediate Uveitis and Related Cystoid Macular Oedema: Evaluation of Macular Morphology and Function with Six-month Follow-up; a Deeper Role of MfERG? Ocul Immunol Inflamm 2022; 30: 234-240.

82) Sudhalkar A, Vasavada A, Bhojwani D, Vasavada V, Vasavada S, Vasavada V, Srivastava S. Intravitreal dexamethasone implant as an alternative to systemic steroids as prophylaxis for uveitic cataract surgery: a randomized trial. Eye (Lond) 2020; 34: 491-498.

83) Gupta A, Ram J, Gupta A, Gupta V. Intraoperative dexamethasone implant in uveitis patients with cataract undergoing phacoemulsification. Ocul Immunol Inflamm 2013; 21: 462-467.

84) Gupta G, Ram J, Gupta V, Singh R, Bansal R, Gupta PC, Gupta A. Efficacy of intravitreal dexamethasone implant in patients of uveitis undergoing cataract surgery. Ocul Immunol Inflamm 2019; 27: 1330-1338.

85) Ragam AP, Kolomeyer AM, Nayak NV, Chu DS. The Use of Ozurdex (Dexamethasone Intravitreal Implant) During Anterior Segment Surgery in Patients with Chronic Recurrent Uveitis. J Ocul Pharmacol Ther 2015; 31: 344-349.

86) Garweg JG, Baglivo E, Freiberg FJ, Pfau M, Pfister IB, Michels S, Zandi S. Response of Postoperative and Chronic Uveitic Cystoid Macular Edema to a Dexamethasone-Based Intravitreal Implant (Ozurdex). J Ocul Pharmacol Ther 2016; 32: 442-450.

87) Cordero-Coma M, Garzo I, Calleja S, Galan E, Franco M, Ruiz de Morales JG. Preoperative cataract surgery use of an intravitreal dexamethasone implant (Ozurdex) in a patient with juvenile idiopathic arthritis and chronic anterior uveitis. J AAPOS 2013; 17: 632-634.

88) Pang JP, Son G, Yoon YH, Kim JG, Lee JY. Combined vitrectomy with intravitreal dexamethasone implant for refractory macular edema secondary to diabetic retinopathy, retinal vein occlusion, and noninfectious posterior uveitis. Retina 2020; 40: 56-65.

89) Santos BBd, Ribeiro Jr MdLB, Barboza MNC, Barioni MFG. Unilateral intravitreal dexamethasone implant for the treatment of cystoid macular edema in intermediate uveitis. Rev Bras Oftalmol 2021; 80: 140-142.

90) Lowder C, Belfort R Jr, Lightman S, Foster CS, Robinson MR, Schiffman RM, Li XY, Cui H, Whitcup SM. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. Arch Ophthalmol 2011; 129: 545-553.

91) Kim DH, Cho BJ, Chung H, Heo JW. Intravitreal Injection of Dexamethasone Implant during Cataract Surgery in Patients with Noninfectious Uveitis. J Kor Ophthalmol Soc 2015; 56: 721-726.

92) Fassbender Adeniran JM, Jusufbegovic D, Schaal S. Common and Rare Ocular Side-effects of the Dexamethasone Implant. Ocul Immunol Inflamm 2017; 25: 834-840.

93) Kumari N, Parchand S, Kaushik S, Singh R. Intractable glaucoma necessitating dexamethasone implant (Ozurdex) removal and glaucoma surgery in a child with uveitis. BMJ Case Rep 2013; 2013: bcr2013201293.

94) Tufail A, Lightman S, Kamal A, Pleyer U, Paniagua NMG, Dot C, Li XY, Jiao J, Lou J, Hashad Y, Grp CS. Post-marketing surveillance study of the safety of dexamethasone intravitreal implant in patients with retinal vein occlusion or noninfectious posterior segment uveitis. Clin Ophthalmol 2018; 12: 2519-2534.

95) Zarranz-Ventura J, Carreno E, Johnston RL, Mohammed Q, Ross AH, Barker C, Fonollosa A, Artaraz J, Pelegrin L, Adan A, Lee RW, Dick AD, Sallam A. Multicenter study of intravitreal dexamethasone implant in noninfectious uveitis: indications, outcomes, and reinjection frequency. Am J Ophthalmol 2014; 158: 1136-1145.e5.

96) Olson DJ, Parhiz AT, Wirthlin RS. Reactivation of Latent Toxoplasmosis Following Dexamethasone Implant Injection. Ophthalmic Surg Lasers Imaging Retina 2016; 47: 1050-1052.

97) Kucukevcilioglu M, Eren M, Yolcu U, Sobaci G. Acute retinal necrosis following intravitreal dexamethasone (Ozurdex(R)) implant. Arq Bras Oftalmol 2015; 78: 118-119.

98) Kim I, Lee J. A Case of Cytomegalovirus Retinitis Following Intravitreal Dexamethasone Implant in

an Immunocompetent Patient with Uveitis. J Kor Ophthalmol Soc 2019; 60: 85-90.

99) Kapoor KG, Colchao JB. Safety of Consecutive Same-Day Bilateral Intravitreal Dexamethasone Implant (Ozurdex). Retin Cases Brief Rep 2020; 14: 200-202.

100) Alba-Linero C, Sala-Puigdollers A, Romero B, Llorenc V, Adan A, Zarranz-Ventura J. Long-Term Intravitreal Dexamethasone Implant Outcomes in Uveitis. Ocul Immunol Inflamm 2020; 28: 228-237.

101) Arcinue CA, Ceron OM, Foster CS. A Comparison Between the Fluocinolone Acetonide (Retisert) and Dexamethasone (Ozurdex) Intravitreal Implants in Uveitis. J Ocul Pharmacol Ther 2013; 29: 501-507.

102) Wang QR, Yang ZY, Zhang WL, Li QH, Kang PD. Abnormal hyperplasia of chondrocytes in a rat model of glucocorticoid-induced osteonecrosis of the femoral head. Eur Rev Med Pharmacol Sci 2022; 26: 6536-6549.

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