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Anatomical and visual outcomes of Retreatment with Intravitreal Dexamethasone Implant versus shifting to intravitreal Aflibercept for refractory Diabetic macular edema after an initial Intravitreal Dexamethasone Implant.

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Short title*:* Intravitreal Dexamethasone Retreatment effects on Diabetic Macular Edema.

ABSTRACT

Purpose: to evaluate the anatomical and visual outcomes of retreatment with repeated intravitreal dexamethasone implants versus repeated aflibercept injections for refractory diabetic macular edema after an initial intravitreal dexamethasone implant.

Subjects and Methods: A retrospective cohort study was done on eyes diagnosed with refractory non-tractional diffuse diabetic macular edema after an initial intravitreal Dexamethasone implant, that had been retreated between 2016 and 2022, and were followed up for 12 months . They were divided into 2 groups. Group A included eyes that had been retreated with Intravitreal Dexamethasone Implants. Group B included eyes that had been retreated with intravitreal Aflibercept injections.

Outcome measures included: changes in central macular thickness, changes in best corrected visual acuity (BCVA), and number of injections of both Dexamethasone implants and Aflibercept during 12 months.

Results: We enrolled a total of 58 eyes. Group A (38 eyes) achieved a CMT reduction 191 ± 100 u, and 4.1 ± 1.1 lines of improvement of BCVA, with 1.7 ±0.8 dexamethasone implant injections. Group B (20 eyes) achieved a CMT reduction 161 ± 84, and 2.0 ± 0.9 lines of improvement of BCVA, with 3.7 ± 1.2 aflibercept injections. Elevated intra ocular pressure happened in 11% of eyes in group A, and in 5% of eyes in group B.

Conclusion: Retreatment with intravitreal dexamethasone implant maybe safe and effective for management of refractory diabetic macular edema after an initial intravitreal dexamethasone implant. It may be more effective than shifting to Aflibercept injections, with much less number of retreatments.

Key words: Intravitreal Dexamethasone Implants, Diabetic macular edema, Anti-VEGF, Aflibercept

INTRODUCTION

Diabetic macular edema (DME) entails macular thickening, that occurs because of microvascular leakage from a disrupted blood-retinal barrier. It may happen during any stage of diabetic retinopathy. [1–3] Mediators for microvascular leakage are all inflammatory, and they include vascular endothelial growth factors (VEGF), intercellular adhesion molecule-1, interleukin-6, monocyte chemotactic protein-1, and leukostasis. [4,5]

Treatment modalities for DME include macular laser photocoagulation, intravitreal steroids, intravitreal anti-VEGF agents, and pars plana vitrectomy with or without internal limiting membrane (ILM) peeling.[4,6–10]

Macular laser photocoagulation (MLP) has been the mainstay treatment for DME. However, during the last decade, MLP has been replaced by anti-VEGF agents [10] like aflibercept, ranibizumab, Brolucizumab, and bevacizumab. [6,11]

Intravitreal Triamcinolone Acetonide (IVTA) has demonstrated anti-inflammatory properties via reducing mediators of inflammation. Although its anti-inflammatory properties have been proven to reduce macular thickness, its

use has been limited due to its effects on intraocular pressure (causes IOP to spike). [12,13]

Intravitreal Dexamethasone implants (DEX) (0.7 mg) (Ozurdex®, Allergan, Inc, Irvine, CA, USA) have a better safety and efficacy profile than the alternative therapies of DME. It is a micronized dexamethasone, that is placed in a biodegradable copolymer of polylactic-co-glycolic acid, which slowly releases dexamethasone into the vitreous over a period of up to six months. Intravitreal DEX implants received FDA approval following the results of the MEAD study[14–18].

Intravitreal injections of Aflibercept (2 mg) (Eylea®, Bayer Pharma AG, Berlin, Germany) have been used with remarkable efficacy for DME after FDA approval in 2014, especially for severe macular thickening and low visual acuity. It is a recombinant FC portion of immunoglobulin G1 fused with VEGF receptors 1 and 2[19–22].

Refractory DME after intra vitreal anti-VEGF agents has been commonly encountered by retina specialists, due to the chronicity of the underlying pathology and the frequency of anti-VEGF treatments. It has been managed by one or more of the following options: Ranibizumab [6,11], Aflibercept [19–22], IVTA [12,13], DEX [14–18], and pars plana vitrectomy [7–9].

However, there is insufficient data about management of **refractory DME after starting an initial Dexamethasone implant therapy**. There is no consensus for a protocol for retreatment of cases that have been previously treated by dexamethasone implant, even though an algorithm had been suggested. [23,24]

Our study focused on 2 specific alternatives for eyes with refractory DME despite an initial dexamethasone implant therapy; retreatment with dexamethasone implants, or shifting to aflibercept retreatment. The aim of our study is to compare both anatomical and visual outcomes between both dexamethasone implants and aflibercept Retreatments.

SUBJECTS AND METHODS

This is a **Retrospective cohort study**. We performed a retrospective review of records for patients with non-tractional diffuse diabetic macular edema (NTDME) that had been treated with Intravitreal dexamethasone implant between 2016 and 2022.

Institutional review board approval was obtained. Approval from the research ethics committee of Faculty of medicine, Cairo University was granted (N-21-2023). The study was registered in clinicaltrials.gov (NCT05847088). Detailed informed consent was waivered as it is a retrospective observational study. This study followed the tenets of the declaration of Helsinki.

Inclusion criteria:

Age 16 years or older, with NTDME that had been previously treated with dexamethasone implant, who received retreatments with ***either*** dexamethasone implant or aflibercept, over a follow up period of 12 months.

Exclusion criteria:

Eyes that didn't receive any retreatment (just a single dexamethasone implant injection) over 12 months, or retreatment with one or more of ; ranibizumab, triamcinolone acetonide, laser therapy, or a pars plana vitrectomy; retreatment with dexamethasone implants or aflibercept with less than 12 months follow up. Combined dexamethasone implant and aflibercept retreatments, or vitrectomized eyes.

Eyes were divided into 2 groups:

Group A: Retreatment with intravitreal Dexamethasone implant injections

Group B: Retreatment with intravitreal Aflibercept injections

All enrolled patients had been subjected to a full ophthalmological examination that included best corrected visual acuity (BCVA) using a decimal chart, intraocular pressure using the applanation tonometry, anterior and posterior segment fundoscopy using slit lamp biomicroscopy, fundus fluorescein angiography, and spectral domain optical coherence tomography (SD-OCT).

Intervention:

Intravitreal Dexamethasone implant (Group A) (DEX) (0.7 mg) (Ozurdex, Allergan, Inc, Irvine, CA, USA) had been performed under aseptic conditions in the operating theatre, under topical anesthesia ± sedation in some cases. The device needle was injected obliquely 3.5 mm from the limbus. Prophylactic antibiotic eye drops (Moxifloxacin 0.5%) were instilled four times daily for a duration of five days. Topical anti-glaucoma eye drops (timolol 5 mg + brinzolamide 10 mg

combination) were administered every 12 hours daily all throughout the follow-up period.

Intravitreal Aflibercept injection (Group B) (2 mg) (Eylea®, Bayer Pharma AG, Berlin, Germany) had been performed with the same technique, and the same post injection treatment as with intravitreal dexamethasone implant.

Follow up had been performed for 12 months. It had been performed **every 4 months** for group A, and **every 2 months** for group B. **Treatment target** was either ≥ 20% reduction in CMT, or ≥ 5 letters of improvement of BCVA (from baseline values).

Indications for retreatment were < 20% reduction in CMT, and < 5 letters of improvement of BCVA (from baseline values).

Study Outcome measures (for each group) included: Change in central macular thickness (CMT) (Baseline and 12 months), change in Best corrected visual acuity (BCVA) (converted into logMAR) (Baseline and 12 months, lines of improvement of BCVA), number of Retreatment injections , number of eyes with the following: CMT change > 100 u, CMT change > 200 u, BCVA change >= 3 lines on the E chart, and complications (in the form of ocular hypertension, sterile iritis, endophthalmitis, and retinal detachment).

Data Analysis:

Statistical analysis was performed using StatPlus software (StatPlus: mac LE, Build 6.1.2/Core v6.1.0, AnalystSoft Inc., Walnut, CA, USA). Descriptive statistics were used to estimate mean ± standard deviation and range for the baseline characteristics. Paired t-test was used to compare between continuous variables and Chi-square test compared between dichotomous variables. P values less than 0.05 were considered statistically significant.

RESULTS

We enrolled 58 eyes of 39 patients after checking both inclusion and exclusion criteria. Group A (Dexamethasone implant) included 38 eyes, and Group B (Aflibercept) included 20 eyes. The baseline demographic and clinical data for both groups are outlined in (Table 1).

Table 1: Baseline demographic and clinical data in both groups

	Group A	Group B	p value
Retreatment	**Dexamethasone Implant**	**Aflibercept**	
sample size	**38**	**20**	
Age	**56 ± 5**	**56 ± 6**	**0.75**
Male / Female	**22/16**	**11/9**	**0.83**
oral / insulin	**15/23**	**3/17**	**0.05**
logMAR BCVA	**0.73 ± 0.26**	**0.83 ± 0.32**	**0.27**
CMT	**493 ± 107**	**496 ± 119**	**0.92**

BCVA*: Best corrected visual acuity

CMT*: Central macular thickness

Group A (Dexamethasone implants Retreatment)

Central macular thickness (CMT) significantly decreased from 493 ± 107 u at baseline to 302 ± 32 u at 12 months (p < 0.0001). The mean CMT change was 191 ± 100 u. CMT change > 100 u occurred in 31 eyes (81.6 %), and CMT change > 200 u was seen in 18 eyes (47.4 %). (Table 2) (Table 3) (Table 5)

Best corrected visual acuity (BCVA) showed a significant improvement from a baseline logMAR 0.73 ± 0.26 to 0.24 ± 0.13 at 12 months (p < 0.0001). The average lines of improvement for BCVA were 4.1 ± 1.1. Improvement of BCVA three or more lines occurred in 35 eyes (92 %). (Table 4) (Table 5)

The average number of dexamethasone implant injections was 1.7 ± 0.8. The maximum number of dexamethasone retreatments was supposed to be 3 injections over the 12 months of follow-up (based on evaluation every 4 months). Three injections were needed in 8 out of the 38 eyes (21%).

No complications were observed except for elevated intra ocular pressure in 4 out of the 38 eyes (11 %)

Group B (Aflibercept Retreatment)

Central macular thickness (CMT) significantly decreased from 496 ± 119 u at baseline to 334 ± 64 u at 12 months ($p < 0.0001$). The mean CMT change was 161 ± 84 u. CMT change > 100 u occurred in 11 eyes (55 %), and CMT change > 200 u was seen in 7eyes (35 %).

(Table 2) (Table 3) (Table 5)

Best corrected visual acuity (BCVA) showed a significant improvement from a baseline logMAR 0.83 ± 0.32 to 0.53 ± 0.31 at 12 months ($p < 0.0001$). The average lines of improvement for BCVA was 2.0 ± 0.9. Improvement of BCVA three or more lines occurred in 6 eyes (30 %). (Table 4) (Table 5)

The average number of aflibercept injections was 3.7 ± 1.2. Three or more injections were needed in 17 out of the 20 eyes (85%). The maximum number of injections was supposed to be 6 injections over the 12 months of follow-up (based on evaluation every 2 months).

No complications were observed except for elevated intra ocular pressure in 1 eye out of the 20 eyes (5 %).

Dexamethasone Implant versus Aflibercept

Dexamethasone implant retreatment resulted in a statistically significant lower CMT at 12 months, than aflibercept retreatment ($p= 0.04$). On the other hand; we cannot confirm that a statistically significant reduction in CMT was achieved by dexamethasone implant compared to aflibercept ($p =0.28$). Larger number of eyes (with dexamethasone implants) achieved >100 u reduction in CMT ($p=0.03$). Higher percentage of eyes with dexamethasone implants experienced >200 u reduction in CMT, however; it is statistically insignificant ($p=0.36$)

(Table 2) (Table 3) (Table 5)

Group A achieved a statistically significant better final logMAR BCVA than group B ($p = 0.0006$). Group A achieved statistically significant more Lines of improvement of BCVA than group B, and a higher percentage achieved 3 or more lines of improvement of BCVA.($p <0.0001$) . (Table 4) (Table 5)

Table 2: Change in central macular thickness in both groups

CMT	Group A	Group B	p value
Baseline CMT	**493 ± 107**	**496 ± 119**	**0.92**
final CMT	**302 ± 32**	**334 ± 64**	**0.04**
p value	**< 0.0001**	**< 0.0001**	

CMT*: Central macular thickness

Table 3: Change in central macular thickness >100 u and > 200 u, in both groups.

CMT change	Group A (n)	Group B (n)	p value
> 100 u	**31 (81.6%)**	**11 (55%)**	**0.03**
> 200 u	**18 (47.4%)**	**7 (35%)**	**0.36**

CMT*: Central macular thickness

Table 4: Change in logMAR Best corrected visual acuity in both groups

logMAR BCVA	Group A	Group B	p value
Baseline	**0.73 ± 0.26**	**0.83 ± 0.32**	**0.27**
final	**0.24 ± 0.13**	**0.53 ± 0.31**	**0.0006**
p value	**< 0.0001**	**< 0.0001**	

BCVA*: Best corrected visual acuity

Table 5: change in outcome measures in both groups

Change	Group A	Group B	p value
CMT	**191 ± 100**	**161 ± 84**	**0.28**
Lines of BCVA	**4.1 ± 1.1**	**2.0 ± 0.9**	**< 0.0001**

BCVA*: Best corrected visual acuity

CMT*: Central macular thickness

Statistically significant lower number of injections (retreatments) were used in group A than in group B, and a lower percentage of eyes required 3 or more injections in group A than in group B ($p < 0.0001$).

There is no statistically significant difference in the incidence of elevated intra ocular pressure during the follow up period between both groups (p=0.47).

DISSCUSSION

Our study is about a "Monotherapy Retreatment" that describes and compares the outcome of *continuing strictly with either* dexamethasone implant retreatments or aflibercept retreatments for refractory diabetic macular edema after an initial dexamethasone implant injection. This may be more elaborative for the validity of management of refractory diabetic macular edema after an initial dexamethasone implant.

Based on our knowledge; there are no studies that tackled shifting to an aflibercept monotherapy after previous dexamethasone implant therapy. Urbancic and coauthors (2021) used a combined dexamethasone- aflibercept regimen for refractory diabetic macular edema after an initial dexamethasone implant injection [25]. An algorithm had been suggested for retreatments after dexamethasone implants; which demonstrated both dexamethasone implant retreatment and the probability of adding a supplementary anti-VEGF at any evaluation point in the treatment [23].

Intravitreal Dexamethasone implant (DEX) is a safe and effective treatment for DME. These implants slowly release dexamethasone into the vitreous over a period of up to six months. Release is more rapid in the first two months, then it becomes gradually slower over the next four months (total six months efficacy)[26]. Several studies including the MEAD study demonstrated an efficient anatomical and functional outcome following DEX implants without any intraocular pressure spikes[14–18]. Dexamethasone targets inflammatory mediators of diabetic macular edema, especially vascular endothelial growth factors (VEGF), intercellular adhesion molecule-1, interleukin-6, monocyte chemotactic protein-1, and leukostasis[4,5].

Our study may provide more insight regarding the effects of DEX implant retreatments on eyes with refractory DME observing a sample size of 58 eyes, over a long follow-up duration (12 months), compared to other studies. [27] we report an average 191 u reduction in CMT using an average 2 dexamethasone implant retreatments over 12 months, which is more favorable than 79 u using 2 implant retreatments over 12 months by Bhandari and coauthors (2022) [28].

Sustained release of dexamethasone causes a prolonged reduction in CMT and improvement of BCVA, without IOP spikes or intractable glaucoma. Retreatment with Dexamethasone implants was administered at four monthly intervals based on the sustained slow release of Dexamethasone[23]. We used a 4-months interval (not a six month interval) for evaluation for retreatment, compared to a 6-months interval that had been used in other studies[23,27].

Previous studies reported that there is an initial high rate of release of dexamethasone over 2 months; followed by a gradually slower release of dexamethasone over the next 4 months[10-14]. In our practice, we didn't find ocular hypertension that would delay our evaluation and probable retreatment (if needed) till 6 months after the previous treatment, so we chose 4 months as an intermediate time interval between the initial 2 months of rapid release and the total 6 months for complete release of dexamethasone. Australian guidelines in 2023 for DME recommend Dexamethasone retreatments in a range 4-7 months (if needed), which is similar to our study[29].

Dexamethasone implants are comparable to Intravitreal Triamcinolone acetonide (IVTA) therapy, which improves DME for a shorter period (half-life of TA is 18.6 days), but

the latter presents with an increased risk of intractable glaucoma[12,13]. In addition, studies reported that Dexamethasone implant is five times more efficient than IVTA[26].

Intravitreal anti-VEGF agents are associated with significant improvement of DME; however, much more frequent injections may be needed, and may reach a plateau effect, which would still be unsatisfactory. An average 1.7 Dexamethasone injections were needed in our study compared to 3.7 aflibercept injections.

Intravitreal aflibercept injection has been used for treatment of refractory diabetic macular edema after previous anti-VEGF treatment. A Study by Salimi and coauthors (2021) reported 119 u reduction in CMT over 12 months using 6 aflibercept injections [22]. Another study by McCloskey and coauthors (2018) reported 117 u reduction in CMT over 12 months using 8.4 injections of aflibercept [21].

Our study observes refractory diabetic macular edema after an initial dexamethasone implant. We report an average 191 u reduction in CMT over 12 months; which demonstrates that retreatment for refractory diabetic macular edema despite a single initial dexamethasone implant may yield a better outcome than for refractory edema after other anti-VEGF initial treatments.

The number of aflibercept retreatment in our study averaged 3.7 over 12 months; which is much less than an average 6 injections over 12 months that were reported by Salimi and coauthors [22], and 8.4 injections over 12 months in other studies like McCloskey and coauthors[21]. We believe this can be attributed to the starting point of retreatment; where we started after an initial dexamethasone implant injection, while the other studies started after multiple initial anti-VEGF injections.

In our study, dexamethasone implant retreatment improved BCVA and CMT more than intravitreal aflibercept, with a much less number of reinjections. We believe that this is a normal cumulative effect because of the sustained release of Dexamethasone, and a potent anti-inflammatory action of dexamethasone [4,5].

Limitation of our study is the retrospective nature of the cohorts and the small sample size. Further studies may be needed that would be: randomized clinical trials, done on larger number of eyes, and for a longer duration of follow up than 12 months.

CONCLUSION

Based on our findings, we recommend using intravitreal dexamethasone implant retreatments for refractory DME after an initial intravitreal dexamethasone implant therapy.

DECLARATIONS

Acknowledgements: None.

Data Availability: All data are included in this article.

Conflict of Interest: Authors declare no conflict of interest.

Ethics Declaration: Institutional review board approval was obtained. Approval from the research ethics committee of Faculty of medicine, Cairo University was granted (N-21-2023). Detailed informed consent was waivered as it is a retrospective observational study. This study followed the tenets of the declaration of Helsinki.

Registration in clinical trials. gov: (NCT05847088)

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