INTRODUCTION

In the western world, diabetic retinopathy is the leading cause of vision loss in the working-age population. Moderate visual loss in patients with diabetic retinopathy is usually caused by diabetic macular edema (DME). Treatment of DME includes focal/grid laser photocoagulation and pharmacologic therapy with intravitreal injection of various anti-vascular endothelial growth factor (VEGF) agents and steroid medications. Among steroid medications, the intravitreal dexamethasone implant (IDI) 0.7 mg (Ozurdex; Allergan, Irvine, CA, USA) is a sustained release device that has been well studied. The side effect profile according
to various studies has demonstrated an increased risk of a generally transiently increase in intraocular pressure (IOP) and of cataract formation, particularly with repeat treatment.\textsuperscript{[11,13‑15]}

In a large randomized clinical trial in patients with DME, Boyer et al found that the IDI 0.7 mg met the primary efficacy endpoint for improvement in best-corrected VA at three years with a safety profile that was acceptable and consistent with previous reports.\textsuperscript{[13]}

Some small retrospective reports have also noted success with IDI for DME and recalcitrant macular edema of other causes.\textsuperscript{[16‑20]}

Vitrectomized eyes are a particularly interesting group to study because the need for vitrectomy in DME is often a marker of resistant edema. Moreover, these eyes may theoretically need more frequent intravitreal anti-VEGF injections due to the lost depot effect of the vitreous. Thus, this group may benefit from an agent such as the IDI for two reasons: (1) Resolution of edema that has become resistant to anti-VEGF therapy (therapeutic response failure) and (2) decreased interval for repeat intravitreal treatments (duration of effect failure). Our hypothesis has been that vitrectomized eyes with DME and suboptimal response to anti-VEGF therapy would respond favorably to IDI implantation and demonstrate improved visual acuity (VA) and reduced central retinal thickness (CRT).

**METHODS**

We performed a retrospective chart review of consecutive cases based on billing records of all patients seen between June 2011 and June 2014 with prior vitrectomy and a diagnosis of DME. Inclusion criteria were age >18 years, a diagnosis of DME, prior vitrectomy, and treatment with IDI at the discretion of the physician for either persistent or recurrent macular edema. All patients meeting the inclusion criteria had received prior anti-VEGF treatment. We recorded demographic information, VA, IOP, and CRT as determined by optical coherence tomography (OCT) measurements, lens status, and the number and type of prior anti-VEGF injections. OCT measurements were performed using the Zeiss Stratus time domain OCT, Zeiss Cirrus spectral domain OCT [Carl Zeiss Meditec, Jena, Germany] or Heidelberg Spectralis spectral domain OCT [Heidelberg Engineering, Heidelberg, Germany].

Primary endpoints of the study were changes in VA and CRT from baseline values to 1 month post-implantation of the device. Secondary endpoints were changes in VA, CRT, and IOP three months after IDI placement. Patients who received additional treatment (either repeat IDI or additional anti-VEGF agents) before 3 months were excluded from our 3-month analysis but included in the 3-month intent-to-treat analysis.

Snellen VA data was converted into logarithm of the minimum angle of resolution (logMAR) notations by standard methods.\textsuperscript{[21]} An approximation of 20/2000 for counting fingers vision at two feet was used in this study.\textsuperscript{[21]}

The Wilcoxon signed-rank test was used for nonparametric paired testing of variables before and after intervention at various time points. Statistical tests were 2-tailed with significance set at 0.05. Stata version 9.0 (StataCorp, LP, College Station, TX, USA) was used for statistical analyses. Institutional Review Board approval was obtained and the study complied with the Health Insurance Portability and Accountability Act of 1996 and adhered to the tenets of the Declaration of Helsinki.

**RESULTS**

Eight eyes of 8 patients met the inclusion criteria. Table 1 shows demographic data of all patients at baseline. Mean logMAR VA was 0.79 ± 0.52 (20/123 Snellen equivalent) and mean CRT was 455.75 ± 123.19 µm at the time of IDI placement. All but one patient was pseudophakic at the time of implantation, and this patient did not develop visually significant cataracts during the study period [Table 1]. An average of 7.00 ± 2.96 anti-VEGF injections and 1.75 ± 1.48 triamcinolone injections had been given prior to IDI implantation.

| Table 1. Baseline characteristics of vitrectomized eyes with recalcitrant diabetic macular edema, treated with intravitreal dexamethasone implant |
|-----------------|---------------|-----------|
| **Category**    | **Unit**      | **Mean±SD**|
| Age             | Years         | 69.18±8.82|
| Visual acuity   | LogMAR        | 0.79±0.52 |
| Central retinal thickness | Microns | 455.75±123.19 |
| Intraocular pressure | mmHg | 18.13±2.32 |
| Anti-VEGF prior to IDI | Injections | 7.00±2.96 |
| Intravitreal triamcinolone prior to IDI | Injections | 1.75±1.48 |
| Time since last treatment | Days | 60.88±32.89 |
| Gender           |               | n         |
| Male             |               | 3         | 37.50 |
| Female           |               | 5         | 62.50 |
| Eye              |               | n         | Percentage |
| Right            |               | 5         | 62.50 |
| Left             |               | 3         | 37.50 |
| IOP medication use |       | 4         | 50.00 |
| No               |               | 4         | 50.00 |
| Lens status      |               | n         | Percentage |
| Phakic           |               | 1         | 12.50 |
| Pseudophakic     |               | 7         | 87.50 |

SD, standard deviation; LogMAR, logarithm of the minimum angle of resolution; IDI, intravitreal dexamethasone implant; Anti-VEGF, anti-vascular endothelial growth factor; IOP, intraocular pressure
Pars plana vitrectomy had been performed for various reasons: Five eyes were operated for persistent DME and three others for non-clearing vitreous hemorrhage. In all eyes treated for persistent DME, peeling of the internal limiting membrane (ILM) assisted with indocyanine green (ICG) was performed.

Though every patient had previously been treated with anti-VEGF agents for DME, the treatment immediately prior to IDI varied, with half receiving anti-VEGF therapy (n = 4) and half receiving intravitreal triamcinolone (n = 4). Anti-VEGF injections immediately prior to IDI included ranibizumab in 2, bevacizumab in 1 and aflibercept in 1 case [Table 2]. The time interval since the most recent treatment was 60.88 ± 32.89 days, which varied based on whether the last treatment was an anti-VEGF agent (47.2 ± 16.7 days) or steroid (74.5 ± 38.9 days).

At 1-month, VA was significantly (p = 0.005) improved from 0.79 ± 0.52 logMAR (20/123) to 0.64 ± 0.55 logMAR (20/88), and CRT was also significantly (p = 0.01) reduced from 455.75 ± 123.19 to 295.00 ± 90.39 µm. Three months after IDI implantation, VA was 0.71 ± 0.56 logMAR (20/103 Snellen equivalent) (p = 0.002) which showed an improvement of 0.08 logMAR compared to pre-treatment VA, and CRT was 335.50 ± 109.17 µm (p = 0.002), representing a reduction of 120.25 µm relative to pretreatment values. Two and 4 patients gained 2 or more lines of vision at 1-month and 3-months, respectively.

IOP did not change significantly at 1 month (p = 0.28) or 3 months (p = 0.48) [Table 3]. IOP increased from 18.13 ± 2.32 to 19.88 ± 3.22 mmHg at 1 month, which was not statistically significant. Two patients required additional topical IOP medications during the course of the study (one patient started latanoprost, and one patient started dorzolamide) but none required additional laser or glaucoma surgery. One patient underwent an additional anti-VEGF injection of aflibercept before 3-months. This patient’s data was included in the 3-month intent-to-treat analysis [Table 3]. This inclusion did not alter any of our results.

### DISCUSSION

This series demonstrates that vitrectomized eyes with persistent or recurrent DME in spite of previous anti-VEGF therapy, respond favorably to subsequent IDI implantation by showing improvement in VA and CRT. These results are consistent with prior small retrospective studies looking at recalcitrant DME. Another important result of the current study is that the duration of the effect of IDI 0.7 mg in vitrectomized eyes with recalcitrant DME is at least 3months. This finding is particularly interesting considering the theoretical need for more frequent intravitreal anti-VEGF injections in vitrectomized eyes. Studies in rabbit eyes have shown a difference in the initial elimination phase of bevacizumab but not ranibizumab after vitrectomy.

Persistence of bevacizumab was longer than ranibizumab in the vitreous cavity of a rabbit model prior to vitrectomy, but was significantly reduced after vitrectomy. This data suggests that there may be a difference in duration of action of bevacizumab but not ranibizumab following vitrectomy. The DRCR.net Protocol I has suggested that at least for ranibizumab, there was no difference in the need for ranibizumab injections over the 3-year study period (Data presented at ASRS 2014 San Diego, CA) in vitrectomized eyes.

The efficacy of the IDI has been compared between vitrectomized and non-vitrectomized eyes. The release rate of the steroid and device efficacy has been similar in vitrectomized and non-vitrectomized eyes in animal

---

**Table 3. Effects of intravitreal dexamethasone implant treatment in vitrectomized eyes**

| Visual acuity | Mean±SD | P  |  |  | Central retinal thickness | Mean±SD | P  |  |  | Intraocular pressure | Mean±SD | P  |  |  | Eyes | n |
|---------------|---------|----|---|---|---------------------------|---------|----|---|---|-------------------|---------|----|---|---|-----|---|
| Initial       | 0.79±0.52 |     |  |  | 455.75±123.19           | 18.13±2.32 | 0.281 | 8 |
| 1 month post-IDI | 0.64±0.55 | 0.005 |  |  | 295.00±90.39           | 19.88±3.22 | 0.281 | 8 |
| 3 months post-IDI | 0.64±0.55 | 0.002 |  |  | 335.50±109.17         | 18.75±3.34 | 0.483 | 8 |

SD, standard deviation; LogMAR, logarithm of the minimum angle of resolution; IDI, intravitreal dexamethasone implant; Anti-VEGF, anti-vascular endothelial growth factor; IVTA, intravitreal triamcinolone acetate
Previous comparative studies evaluating IDI for DME have also found comparable VA and CRT changes in non-vitrectomized and vitrectomized eyes.

Side effects of IDI treatment in our study are consistent with previously published works including a transient non-significant increase in IOP. While two patients in our study required additional IOP-lowering medications, none required laser treatment or filtration surgery, and no significant cataract progression was seen.

There are several limitations to this study. It is retrospective in nature and lacks a pre-specified protocol to guide the time for switching to IDI placement. However, our data suggested consistency in the practice pattern of the treating physicians as the switch to IDI was made typically when no VA or CRT improvement occurred following anti-VEGF treatment immediately prior to IDI implantation. There were no strict VA or CRT criteria, and the conversion was at the discretion of the physician, which is a limitation of this study that should be addressed in prospective studies. Follow-up duration after IDI placement varied based on the treating physicians’ practice pattern, which limited analysis of secondary endpoint data. Another shortcoming was that three different OCT machines were used in the study; although this would incur some inaccuracy in mean CRT values, but since the same device was used for pre- and post-treatment CRT comparisons in any given patient, this issue should probably have a small effect on paired statistical analyses. One patient received an injection of aflibercept before 3 months transpired. Intent-to-treat analysis versus exclusion of this patient did not alter our results. Half of the patients in our series had received intravitreal triamcinolone prior to switching to IDI. The efficacy of triamcinolone varies from patient to patient, and it is unclear what the “washout” period should be to identify the pure effects of IDI. Our intervals ranged from 42 to 140 days—certainly over a month—and while this remains a potential limitation, it is reflective of “real-life” situations in clinical practice. Another limitation of the current study is short follow-up. Studies with longer follow-ups are warranted to better clarify the longer-term effects of IDI in vitrectomized eyes.

In summary, this study suggests that the intravitreal dexamethasone implant can improve VA and reduce CRT in vitrectomized eyes with persistent or recurrent DME and prior anti-VEGF therapy; these improvements last for at least three months.

Financial Support and Sponsorship
Nil.

Conflicts of Interest
There are no conflicts of interest.

REFERENCES

1. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin epidemiologic study of diabetic retinopathy. XV. The long-term incidence of macular edema. Ophthalmology 1995;102:7-16.

2. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124-136.

3. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117:1064-1077.e35.

4. Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. Early Treatment Diabetic Retinopathy Study Research Group. Arch Ophthalmol 1985;103:1796-1806.

5. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: Results from phase II 3 randomized trials: RISE and RIDE. Ophthalmology 2012;119:789-801.

6. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Sehlingemann RO, et al. The RESTORE study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615-625.

7. Do DV, Schmidt-Erfurth U, Gonzalez VH, Gordon CM, Tolentino M, Berliner AJ, et al. The DA VINCI Study: Phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. Ophthalmology 2011;118:1819-1826.

8. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: Report 2. Ophthalmology 2010;117:1078-1086.e2.

9. Gillies MC, Simpson JM, Gaston C, Hunt G, Ali H, Zhu M, et al. Five-year results of a randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema-related central retinal vein occlusion. Ophthalmology 2010;117:2453-2460.

10. Haller JA, Bandello F, Belfort R Jr., Blumenkranz MS, Gillies M, Heier J, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion: Twelve-month study results. Ophthalmology 2011;118:1134-1146.e3.

11. Haller JA, Bandello F, Belfort R Jr., Blumenkranz MS, Gillies M, Heier J, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology 2010;117:1134-1146.e3.

12. Boyer DS, Yoon YH, Belfort R Jr., Bandello F, Maturi RK, Augustin AJ, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014;121:1904-1914.

13. Meyer LM, Schönfeld CL. Secondary glaucoma after intravitreal dexamethasone 0.7 mg implant in patients with retinal vein occlusion: A one-year follow-up. J Ocul Pharm Ther 2013;29:560-565.

14. Querques L, Querques G, Lattanzio R, Gigante SR, Del Turco C, Corradetti G, et al. Repeated intravitreal dexamethasone implant (Ozurdex®) for retinal vein occlusion. Ophthalmologica 2013;229:21-25.

15. Mayer WJ, Wolf A, Kernt M, Kook D, Kampik A, Ulbig M, et al. Twelve-month experience with Ozurdex for the treatment of macular edema associated with retinal vein occlusion. Eye (Lond) 2013;27:816-822.

16. Pacella E, Vestri AR, Muscella R, Carbotti MR, Castellucci M, Coi L, et al. Preliminary results of an intravitreal dexamethasone implant (Ozurdex®) in patients with persistent diabetic macular edema. Clin Ophthalmol 2013;7:1423-1428.

17. Rishi P, Rishi E, Kuniyal L, Mathur G. Short-term results of
intravitreal dexamethasone implant (OZURDEX®)) in treatment of recalcitrant diabetic macular edema: A case series. Oman J Ophthalmol 2012;5:79-82.

18. Guigou S, Hajjar C, Parrat E, Merie PY, Pommier S, Matoniti F, et al. Multicenter Ozurdex® assessment for diabetic macular edema: MOZART study. J Fr Ophthalmol 2014;37:480-485.

19. Dutra Medeiros M, Postorino M, Navarro R, Garcia-Arumí J, Mateo C, Corcóstegui B. Dexamethasone intravitreal implant for treatment of patients with persistent diabetic macular edema. Ophthalmologica 2014;231:141-146.

20. Lazic R, Lukic M, Boras I, Draca N, Vlasic M, Gabric N, et al. Treatment of anti-vascular endothelial growth factor-resistant diabetic macular edema with dexamethasone intravitreal implant. Retina 2014;34:719-724.

21. Holladay JT. Proper method for calculating average visual acuity. J Refract Surg 1997;13:388-391.

22. Ahn J, Kim H, Woo SJ, Park JH, Park S, Hwang DJ, et al. Pharmacokinetics of intravitreally injected bevacizumab in vitrectomized eyes. J Ocul Pharmacol Ther 2013;29:612-618.

23. Ahn SJ, Ahn J, Park S, Kim H, Hwang DJ, Park JH, et al. Intraocular pharmacokinetics of ranibizumab in vitrectomized versus nonvitrectomized eyes. Invest Ophthalmol Vis Sci 2014;55:567-573.

24. Christoforidis JB, Williams MM, Wang J, Jiang A, Pratt C, Abdel-Rasoul M, et al. Anatomic and pharmacokinetic properties of intravitreal bevacizumab and ranibizumab after vitrectomy and lensectomy. Retina 2013;33:946-952.

25. Chang-Lin JE, Burke JA, Peng Q, Lin T, Orilla WC, Ghosn CR, et al. Pharmacokinetics of a sustained-release dexamethasone intravitreal implant in vitrectomized and nonvitrectomized eyes. Invest Ophthalmol Vis Sci 2011;52:4605-4609.

26. Medeiros MD, Alkabes M, Navarro R, Garcia-Arumí J, Mateo C, Corcóstegui B. Dexamethasone intravitreal implant in vitrectomized versus nonvitrectomized eyes for treatment of patients with persistent diabetic macular edema. J Ocul Pharmacol Ther 2014;30:709-716.

27. Bonnin S, Dupas B, Sanharawi ME, Perol J, Erginay A, Tadayoni R, et al. Efficacy of dexamethasone intravitreal implant for the treatment of diabetic macular edema. Eur J Ophthalmol 2015;25:448-453.

28. Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh H, Li XY, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina 2011;31:915-923.