Short term comparison results between two eyes of same individual treated with Dexamethasone implant and Ranibizumab in the management of naive Diabetic Macular Edema (DME).

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Abstract

Objective: To compare the effect of intravitreal dexamethasone implant and intravitreal Ranibizumab in paired eyes of patients with naive diabetic macular oedema.

Method: Prospectively patients with bilateral symmetrical centre involving newly diagnosed diabetic macular oedema are assigned randomly to receive intravitreal Ranibizumab monthly for three months in one eye and intravitreal dexamethosone implant in the other. During follow ups, patients were looked for functional and structural changes.

Results: Twenty eyes of ten patients were included in the study. Eyes in the dexamethasone arm showed an improvement in visual acuity from mean 0.44 to 0.13 and central foveal thickness reduced from mean 412.5 um to 255 um which was comparable to paired eye RZB arm in which vision improved from 0.48 to 0.13 and CMT from 413 um to 262 um and took one third lesser number of injections than RZB arm.

Summary: The results from our study clearly compares the effects of intravitreal Dexamethasone to intravitreal Ranibizumab and shows that patients treated with DEX implant achieved statistically significant and clinically meaningful visual improvements with lesser number of injections than RZB. Our data support the use of DEX implant as first line agent in the treatment of patients with DME.

Keywords: DME: Diabetic Macular Edema, DEX: Dexamethasone implant, RZB: Ranibizumab, visual acuity, Central macular thickness.

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Introduction

Diabetic macular edema (DME), defined as retinal thickening in the posterior pole, resulting from retinal vascular hyper permeability and other alterations in the retinal microenvironment, and represents a common cause of vision loss among diabetics. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) estimate that after 15 years of known diabetes, the prevalence of diabetic macular edema is approximately 20% in patients with type 1 diabetes mellitus (DM), 25% in patients with type 2 DM who are taking insulin and 14% in patients with type 2 DM who do not take insulin. Severity of DME in the International Clinical Diabetic Macular Edema Disease Severity Scale is based solely on whether retinal thickening and hard exudates involve or threaten the center of the macula, reflecting the importance of foveal involvement for prognosis and management [1].

The exact aetiology of DME is still not clear; it is believed that inflammation plays an important role in disease development. Progressive hypoxia leads to increase in permeability of macular capillaries which leads to increased levels of vascular endothelial growth factors (VEGF) and release of inflammatory factors including chemokines, cytokines such as interleukin (IL-6) and IL-8, and prostaglandins [2,3]. This in turn may cause loss of endothelial cells and pericytes.

With above pathogenesis, intravitreal anti VEGF's has been efficiently used in the management of DME. Nonetheless few patients show reduced response and also the compliance to the treatment is very less due to frequent injections [4,5]. It is also known that corticosteroid reduces capillary permeability and the formation of secondary macular oedema of various etiologies [6,7]. They also prevent the migration of leucocytes and formation of VEGF factor. It was in 2014 intravitreal dexamethasone implant was approved by FDA for use in DME. But still use of intravitreal steroids is limited to recalcitrant DME and DME in psuedophakic patients.

We also know that there are many other systemic risk factors which affect the progression of diabetic retinopathy and diabetic maculopathy like hypertension, dyslipedemia, nephropathy, smoking, alcohol consumption, body mass index and so on. Including two eyes for comparison of same patient will remove differences in these factors. So our study included a cohort of patients with naive diabetic macular oedema involving centre of the macula which is symmetrical in two eyes in terms of visual acuity and central macular thickness. One eye received intravitreal anti VEGF (Ranibizumab) and other eye received intravitreal Dexamethasone implant.

Method

This is a prospective interventional study were 10 patients with naive diabetic macular oedema were included in the study who were further randomly divided into two arms, one arm receiving intravitreal Ranibizumab (Lucentis) and second arm receiving intravitreal Dexamethasone impalnt (Ozurdex). The two eyes were matched with visual acuity and a central macular thickness difference of not more than 50 microns. All 10 patients in the study were phakic patients with clear lens status.

Randomly one eye of the patient received Ranibizumab and after 1 week other eye received DEX implant. Every 4 week follow ups were done for 3 months and at every visit, VA, CMT, and IOP were evaluated. Snellen best corrected visual acuity (BCVA) was measured at each visit. CMT was evaluated by optical coherence tomography (OCT) (Appasamy associates), and IOP was measured using a Goldman's applanation tonometer.

Patients were excluded from the study if they don't match any of the inclusion criteria. If they had received previous intravitreal injections or laser treatment and if they have any additional retinal vascular pathology like vein or arterial occlusions. Patients were also excluded if they didn't keep up the follow up visits and who had very poor systemic sugar controls (HbA1c>9). Patients with elevated IOP or known glaucoma patients with disc changes or visual field changes or patients with known steroid responders were also excluded.

Pre informed consent was taken from all the patients for including them into the study. The study received approval from the local ethical committee and it adhered to the tenets of the Declaration of Helsinki.

Data analysis

All the details were gathered and entered into Microsoft office spreadsheet and analysed. Statistical significance was set at <0.05.

Results

Ten consecutive patients were identified with bilateral, symmetric DME as defined above – this cohort involved ten eyes treated with the DEX implant and the ten paired contralateral eyes treated with RZB for the same 3-month period.

Table 1. *Demographic data analysis of the study population.*

Demogarphy	Numbers
Mean Age in years	56.9 (52-72)
Sex	
Male	7
Female	3
HbA1c mean	7.47 (5.9- 8.9}

Details regarding to structure of study population are explained in Table 1. Mean age group in the study population was 56.9 years with seven males and three females being nominated. An average duration of diabetes of all patients being 14.3 years. Patient's glycosalated hemoglobin was checked at the time of inclusion into the study and taken as baseline reading (mean: 7.47, range: 5.9-8.9). Other baseline parameters read were VA, CMT, and IOP and are shown in Table 2. No significant difference was noted between DEX eyes and RZB eyes in regard to mean logMAR VA (0.44 and 0.48, respectively; p=0.294, Mann-Whitney U-test), mean CMT (412.5 and 413 µm, respectively; p=0.795), and mean IOP (16.6 and 15 mmHg, respectively; p=0.535).

Table 2. *Features of matched control eyes at the initiation of treatment.*

Parameters	Intravitreal Dexamethasone	Intravitreal Ranibizumab	p value
Laterality			
Right eye	5 (50)	5 (50)	-
Left eye	5 (50)	5 (50)	-
Lens status			
Phakic	7 (70)	8 (80)	-
Pseudophakic	3 (30)	2 (20)	-
Central macular thickness Mean	412.5 um	413 um	0.733
Visual acuity Mean in log MAR	0.44	0.48	0.223
IOP in mm of hg Mean	16.6	16.2	0.523

All the data of each patient on all the visits in each arm were entered in the Tables 3 and 4. Treatment outcomes in each arm were compared to study baseline from visits at Month 1, Month 2, and Month 3 and are presented in Table 5. Lens status during all follow ups in both the arms remained clear in both the arms at the end of 3 months. In terms of VA, both the DEX and RZB arms improved during the study period, with gains in mean logMAR VA of 0.31 and 0.35, respectively, which was statistically significant (p=0.004, and p=0.006) but no significant difference noticed between the two arms (p=0.156 Wilcoxon signed rank test).

CMT decreased during the study period in both the DEX arm and the RZB arm (net decrease of 157.5 versus 151 µm, respectively), although these differences did not differ significantly (p=0.112, Mann-Whitney U-test). However, improvement in mean CMT in both arms achieved statistical significance from baseline to Month 3 (p=0.006 DEX arm and p=0.002 RZB arm, Wilcoxon signed rank test). The greatest difference in mean CMT between the two study arms was seen at Month 2, when the mean CMT for the DEX arm improved to 275 µm (from 323 µm; p=0.057).

No patients were lost to follow-up during the study period. No significant complications, including infectious endophthalmitis, vitreous hemorrhage, retinal detachment, or lens disruption/subluxation, were noted for either treatment arm during the study period. In eyes that received the DEX implant, only one eye demonstrated IOP 24 mmHg at any time point, and got normalized by the end of the study period with just topical IOP lowering medication. No eyes in the RZB arm demonstrated elevation of IOP.

Table 3. *Dexamethasone implant group.*

S.No	Age	Sex	Eye	Diagnosis	Parameters			1 Month			2 Months			3 Months		
					VA	IOP	CMT	VA	IOP	CMT	VA	IOP	CMT	VA	IOP	CMT
1	57	M	R	SNPDR	0.4	18	370	0.2	16	310	0.1	16	270	0.1	16	250
2	56	F	L	SNPDR	0.6	16	480	0.4	18	390	0.3	18	320	0.2	14	280
3	54	M	R	SNPDR	0.5	14	430	0.3	14	330	0.2	16	270	0.1	16	250
4	58	M	L	MNPDR	0.3	16	340	0.2	16	280	0.2	16	250	0.1	16	240
5	52	M	R	VSNPDR	0.5	18	450	0.3	18	330	0.2	18	290	0.2	16	260
6	60	F	L	SNPDR	0.4	20	400	0.2	24	300	0.1	20	260	0.1	18	250
7	62	M	R	MNPDR	0.3	16	330	0.2	14	270	0.2	16	250	0.1	18	240
8	57	M	L	VSNPDR	0.4	18	410	0.2	16	320	0.2	18	270	0.1	18	250
9	55	F	R	SNPDR	0.5	14	455	0.3	18	340	0.2	20	290	0.1	18	270
10	58	M	L	SNPDR	0.5	16	460	0.3	16	360	0.2	16	280	0.2	16	260
Average	56.9	M-7 F-3	R-5 L-5	SNPDR-6 VSNPDR-2 MNPDR-2	0.44	17	413	0.26	17	323	0.19	17	275	0.13	16.6	255

*Age in years, VA: Visual Acuity in decimal LogMAR; CMT: Central Macular Thickness in Microns; SNPDR: Severe Non-Proliferative Diabetic Retinopathy; MNPDR: Moderate Non-Proliferative Diabetic Retinopathy; VSNPDR: Very Severe Non-Proliferative Diabetic Retinopathy.

Table 4. *Ranibizumab group.*

S.No	Age	Sex	Eye	Diagnosis	Parameters			1 Month			2 Months			3 Months		
					VA	IOP	CMT	VA	IOP	CMT	VA	IOP	CMT	VA	IOP	CMT
1	57	M	L	SNPDR	0.5	16	400	0.3	16	320	0.2	14	280	0.1	16	260
2	56	F	R	SNPDR	0.5	18	380	0.4	16	350	0.3	16	300	0.2	14	280
3	54	M	L	SNPDR	0.4	14	360	0.3	14	300	0.2	18	260	0.1	16	240
4	58	M	R	MNPDR	0.4	16	390	0.3	18	310	0.2	16	270	0.1	16	250
5	52	M	L	VSNPDR	0.5	14	450	0.4	16	380	0.3	14	300	0.2	16	280
6	60	F	R	SNPDR	0.5	16	430	0.4	14	360	0.2	16	290	0.1	18	270
7	62	M	L	MNPDR	0.4	18	370	0.3	16	300	0.2	16	270	0.1	16	240
8	57	M	R	VSNPDR	0.5	16	440	0.3	18	330	0.3	18	300	0.2	16	280
9	55	F	L	SNPDR	0.6	18	480	0.4	14	380	0.2	14	300	0.1	16	260
10	58	M	R	SNPDR	0.5	16	430	0.3	16	320	0.2	16	290	0.1	14	260
Average	56.9	M-7 F-3	R-5 L-5	SNPDR-6 VSNPDR-2 MNPDR-2	0.48	16	413	0.34	16	335	0.23	16	286	0.13	15.8	262

*Age in years, VA-Visual Acuity in decimal LogMAR, CMT-Central Macular Thickness in microns. SNPDR- Severe Non-Proliferative Diabetic Retinopathy, MNPDR-Moderate Non-Proliferative Diabetic Retinopathy, VSNPDR- Very Severe Non-Proliferative Diabetic Retinopathy

Table 5. *Treatment outcomes - baseline, Months 1-3.*

Parameters	Intravitreal Dexamethasone N=10	Intravitreal Ranibizumab N=10	Standard deviation	p value
Mean VA logMAR Baseline	0.44	0.48	0.0966, 0.0632	0.168
1 month	0.26	0.34	0.0699, 0.0527	0.004
2 month	0.19	0.23	0.0568, 0.0483	0.037
3 month	0.13	0.13	0.0483, 0.0483	1
Net gain in VA	0.31	0.35		0.156
P Value baseline to 3 months	0.004	0.006	-	-
Mean CMT in um Baseline	412.5	413	52.02, 38.88	0.976
1 month	323	335	35.91,30.64	0.333
2 month	275	286	21.21, 15.05	0.057
3 month	255	262	12.69, 15.49	0.132
Net decrease in CMT	157.5	151	-	0.122
P Value baseline to 3 months	0.006	0.002	-	-

*CMT: Central Macular Thickness; DEX: Dexamethasone; logMAR: Logarithm of the Minimum Angle of Resolution; RZB: Ranibizumab; SD: Standard Deviation; VA: Visual Acuity.

Discussion

Treatment of diabetic macular oedema has been evolving with increasing understanding of the pathological mechanisms underlying the disease and also the increase in therapeutic agents. With availability of newer lasers like subthreshold micro pulse and yellow laser, focal laser still remain treatment of choice in non centre involving macular oedema. But in patients with centre involving macular oedema the use of intravitreal injections of anti-VEGF medication, and the Dexamethasone implant has shown increased efficacy in numerous studies [5-17].

Studies of the pathological microenvironment of DR and DME have revealed a highly complex picture of the signals that drive vascular permeability and lead to macular edema [5]. Our study was unique in taking a cohort of patients with paired eyes of same individual having symmetric DME which have not been subjected to any other treatments before. This cohort explained for some of the complex ecological influences that drive DME, such as patient compliance, testing conditions, treatment procedures, and of course the effects of systemic diabetic control.

There are many studies which confirmed effectiveness of dexamethasone implant in reducing recalcitrant DME [18-22], our study showed dexamethasone implant has same or better effect when compared to anti-VEGF therapy in an extremely controlled manner in contralateral eyes of the same patients with naive DME eyes matched for VA and CMT. In this series, a cohort of patients was identified whose response to the DEX implant in terms of improved VA and CMT reduction was found to be equivalent to that seen with anti-VEGF use in the contralateral eye, in the short term.

When improvement is visual acuity was assessed, marked improvement was seen in dexamethasone arm in second and third month (p=0.004 and p=0.037 respectively) though the final visual gain was comparable between the arms. Similar kind of observations were reported in previous other studies who found better visual acuity improvement in naive eyes than in non-naive eyes and more in second and third month [23]. In our study by and large the gain in visual acuity was 60% and 62% in the two arms, DEX and RZB respectively which is in line with those previously published [24-27].

The overall difference in CMT reduction between the two arms did not achieve statistical significance (0.122) but the greatest significant difference was noted at Month 2, consistent with prior studies that have demonstrated a peak effect for the DEX implant at around 2-3 months post-treatment [28]. Overall, the improved clinical response of this cohort supports the use of a single injection of the DEX implant to treat a subset of DME patients.

Eyes in the DEX arm received one-third the number of intravitreal injections as their paired, contralateral eyes, and patients found the potential reduced treatment burden to be an advantage. With the very low incidence of post-injection endophthalmitis seen in large trials with the DEX implant [29-31], fewer injections may offer a safer, less morbid alternative in appropriate patients, and result in equal or greater efficacy in reducing CMT.

No significant complications associated with the intravitreal injections given in either arm of the trial were encountered. A modest, transient elevated IOP was seen in two eyes that received injection of the DEX implant, each of which was treated with IOP-lowering medication for 1-2 months followed by a return to normal IOP and discontinuation of topical therapy.

The current study is limited by its small size and short follow-up. Large prospective, randomized studies, with larger sample sizes and correlations with intravitreal cytokine profiles, will be better able to identify the population of DME patients who may best respond to steroid formulations, anti-VEGF agents, or both as clinicians seek to optimize their treatment regimens.

In the current clinical environment, there is increasing support from the published literature for a transition from intravitreal anti-VEGF therapy to the use of intravitreal sustained-release steroids as first-line DME treatment. But, subsequent follow-up of the Ranibizumab groups in Protocol I demonstrated sustained improvement in median and mean vision up to five years with a reduced treatment burden down to a median of 0-1 injection in the 4^{th} and 5^{th} years of follow-up. So the longer follow ups of both the arms might be crucial for the conclusion. The current study supports the idea that other inflammatory pathobiologic pathways contribute to DME, and

that these may be responsive targets for intravitreal steroid treatment.

Importantly, the study does so with a consecutive head-to-head comparison of contralateral eyes that controls for any variability in patient glycemic and blood pressure control, genetics, idiosyncratic responses to therapy, and compliance with follow-up and treatment, factors known to potentially contribute to the considerable variability seen in the outcomes of intravitreal therapy for retinal vascular disease. Within the complex pathological setting of DME, the DEX implant should be considered strongly as an alternate first line therapeutic agent.

Conclusion

The results from our study clearly compares the effects of intravitreal Dexamethasone to intravitreal Ranibizumab and shows that patients treated with DEX implant achieved statistically significant and clinically meaningful visual improvements with lesser number of injections than RZB. Our data support the use of DEX implant as first line agent in the treatment of patients with DME.

Financial Interest

None financial disclosures.

Conflicts of Interest

Conflicts of interest none with any of the authors.

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