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A retrospective, non-randomized, clinical review on the effect of single-dose biosimilar Razumab injection in diabetic macular edema

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Abstract: Diabetic macular edema (DME) is one of the microvascular complications of diabetes and also coexists with diabetic retinopathy. The present study aims to investigate the effectiveness of single-dose biosimilar Razumab injection in diabetic macular edema. In this retrospective, non-randomized, clinical review on patients (n=50), 50 eyes with diabetic macular edema were selected and treated with a single dose of 2.3mg/0.23mL Razumab injection intravitreally. Visual acuity (VA) and macular thickness (MT), were evaluated for a period of up to 45 days after injecting biosimilar Razumab and were used to assess the effectiveness after treatment for 45 days. The results of the study showed that there was a significant increase in visual acuity and a marked reduction in macular thickness and the intraocular pressure (IOP) and anterior segment (AS) examination reverted to normal after the injection (Day 45). This study concludes that a single dose of biosimilar Razumab injection was effective in improving visual acuity and reducing macular thickness with no ocular concerns in diabetic macular edema patients.

Introduction

The prevalence of diabetes mellitus and its complications are rising all over the world (Verma et al., 2021). In India, approximately 77 million population are affected with diabetes (Raman et al., 2022). Among the microvascular complications, diabetic retinopathy (DR) is the primary cause of visual impairment in diabetic patients and its prevalence rate is 16.9% (Vashist et al., 2022). The epidemiological data on DME is comparatively paucity. A review conducted in 2012 showed that up to 7% of people with diabetes might be affected by DME and its risks are greatly similar to DR (Lee et al., 2015). Also, the prevalence of diabetic macular edema increased from 0% to 3% population who were recently diagnosed with diabetes and about 28% to 29% in those with known cases of diabetes for more than 20 years (Preethi et al., 2021).

Diabetic macular edema (DME) is a common sight-threatening complication of diabetes, which causes preventable blindness in the population all over the world. It arises as retina thickening because of blood-retinal barrier failure, which causes fluid accumulation in the macula, a portion nearly the central retina. It can coexist with any severity level of diabetic retinopathy (DR) (Giridhar et al., 2021; Schmidt-Erfurth et al., 2017).

Criteria to be achieved for diagnosing clinically significant macular edema which is one of the types of DME were retinal thickening at or within 500 µm of the macula center and/or any hard exudates at or within 500 µm of the macula center if associated with adjacent retinal thickening (excluding residual hard exudates

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remaining after retinal thickening has disappeared) and/or a zone(s) of 1 disc area or larger retinal thickening, any part within 1 disc diameter of the macula center (Mathew et al., 2015).

A Vascular Endothelial Growth Factor (VEGF) is a primary regulator responsible for vasculogenesis and angiogenesis in the eye. VEGF is classified into 5 types such as VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E. Mainly, VEGF-A is associated with macular edema development compared to the other types (Kartasasmita et al., 2018; Scholl et al., 2010).

Anti-VEGF drugs such as ranibizumab, bevacizumab, pegaptanib, and aflibercept are one of the primary standard treatments for DME (Pożarowska and Pożarowski, 2016). An intravitreal ranibizumab is a fully recombinant humanized monoclonal antibody (Fab), which has emerged as an effective and well-tolerated treatment for retinal vascular diseases (Ferrara et al., 2006; Massin et al., 2010). It acts by binding to the receptor site of all the VEGF-A isoforms, this prevents vascular leakage, endothelial cell proliferation, and new blood vessel formation.

As ranibizumab (Lucentis) is an expensive drug. In 2015, the Drug Controller General of India approved the first ophthalmic biosimilar ranibizumab (Razumab 10mg/ml) injection, which was developed as a cost-effective drug by Intas Pharmaceuticals Ltd., Ahmedabad, India.

A biosimilar Razumab is a drug that imitates the overall efficacy and safety of its referral drug (Ranibizumab) only there would be slight changes in its basic structure and functions (Gopal et al., 2020). Their molecular weight is 48kDa (Ratra et al., 2022).

The study aimed to assess the effectiveness of single-dose razumab injection in diabetic macular edema by evaluating the visual acuity and macular thickness changes for up to a period of 45 days.

Materials and Methods

It was a retrospective, non-randomized, clinical review on the effect of single-dose biosimilar razumab injection in diabetic macular edema in a tertiary care hospital, Salem. The cases were taken from the medical record department of the tertiary care hospital, Salem. The study was conducted for a period of 6 months from Jan to Jun 2022 on the patients admitted to the ophthalmology department of the tertiary care hospital during the period of Jan to Dec 2021.

Patients were selected based on inclusion criteria such as the patient with type II diabetes mellitus; who initiated Razumab for the first time; with impaired VA of 6/60-6/18 Snellen equivalent, with macular thickness ≥ 200µm; the age of ≥ 40 years.

The exclusion criteria are the patients who have a suspected infection, or inflammation in and/or around the eye; Previous laser or anti-VEGF treatment in the study eye before 3 months; pregnant and breastfeeding patients; with uncontrolled glaucoma. The ocular examination performed involved best-corrected visual acuity (BCVA) being measured using Snellen's charts and converted to Logarithm of the Minimum Angle of Resolution (log MAR) visual acuity for statistical analysis; the anterior segment being examined using a slit lamp biomicroscope; and macular thickness being measured using optical coherence tomography.

Data were collected from pre-injection to day 45. Visual acuity (Snellen charts) was converted to log MAR chart values using the formula of

$$Log\ MAR = \frac{Snellen\ numerator}{Snellen\ denominator}.$$

A Log MAR is a chart that is highly recognized as providing the most reliable results compared to other charts like Snellen's chart. In this study, for statistical purposes, we needed to convert the Snellen charts to the Log MAR chart. The mean and median were found for visual acuity, macular thickness, and IOP in an Excel sheet. The percentage of improvement was calculated by using the formula of

$$\%\ of\ improvement = 100 \times \frac{final - initial}{initial}.$$

The statistical analysis was done by using a Paired T-test. The p-value at $p \leq 0.05$ is significant, at $p \leq 0.01$ highly significant, and at $p \leq 0.001$ very highly significant. The results were tabulated using a simple statistical method of Minitab version 2019.

Results

In this study, fifty eyes of 50 patients with diabetic macular edema were enrolled to assess their visual acuity and macular thickness to determine the overall effectiveness of single-dose biosimilar Razumab injection. All of them received a single dose of intravitreal Razumab injections for their DME. There were 28 right eyes and 22 left eyes. Twenty-eight (56%) and twenty-two (44%) were females and males respectively.

The mean pre-injection visual acuity was 0.891±0.195 (range 0.47-1.17). On day 1 of injection, the visual acuity was 0.891±0.195 (range 0.47-1.17) with 1.14% improvement. On day 7 it was 0.8794±0.199 (range 0.47-1.17) with a decreased visual acuity % of -0.02, with no significant improvement from day 1. On day 14, it was 0.742± 0.211 (range 0.17-1.07) showing an improvement

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of 15.31%, and on day 30, it was 0.695± 0.211 (range 0.17-1.07) with a 21.22% improvement, and on day 45, it was 0.695 ±0.211 (range 0.17-1.07) with 21.22% improvement. The improvement in visual acuity at day 45 compared with the pre-injection was statistically significant (<0.001***). Table 3 shows the log MAR BCVA.

Table 1. Analysis of studied cases according to demographic details

Demographic data		N (%)
Gender	Female	28 (56%)
	Male	22 (44%)
Eye	Right	28 (56%)
	Left	22 (44%)
Age (years)	41-50	11 (22%)
	51-60	15 (30%)
	61-70	48 (48%)

The mean pre-injection macular thickness as per OCT was 403.3±88.59µm (298-721). After day 14, the mean macular thickness was 360.7 ± 87.78µm (range 266-685) with a 4.49% improvement, on day 30, it was 358.2 ± 87.41µm (range 240-650) with an 11% improvement, and on day 45, it was 339.4 ± 85.93 µm (range 222-611) with 15.7% improvement (Table 3). The decrease in macular thickness at day 45 compared with the pre-injection was statistically significant (<0.001***).

The mean pre-injection IOP as per the applanation tonometer was 15.84 ± 2.427mmHg (range 12-20). On day 1, it was 16.56 ± 3.156mmHg (range 12-24), which shows the increase in the IOP range. On day 7 the mean was 14.68 ±2.113mmHg (range 11-19), which shows that the IOP range reverts to normal. Table 4 shows, that the decrease in the IOP range on day 7, compared with day 1 was statistically significant (<0.001***).

Table 5 shows, Anterior segments of the patients were evaluated as per slit lamp examination. On day 1 of injection, 26 (52%) patients had a suprachoroidal haemorrhage, and 24 (48%) were normal. On day 7 of post-injection, all 50 patients showed normal results in AS Examination.

Discussion

In DME, due to vasogenic or cytogenic processes lead to fluid accumulation in the intracellular and extracellular spaces (Chen et al., 2020; Romero-Aroca et al., 2016). Depending on the location, there are different macular edema patterns discussed by Otani et al. (1999). After anti-VEGF injections, Research has found incredible predicated results for anatomic and functional development in several groups (Buabbud et al., 2010; Itoh et al., 2016; Radovanova, 2014; Seo et al., 2016).

According to the total number of DME patients, intravitreal injection was administered to a higher number of female patients compared to male patients, which correlates with Sharaf et al. (2015b). Most of the patients are in the age group of 61-70 (n=48).

The mean log MAR BCVA was improved from pre-injection (0.891) to day 45 (0.695). which showed similar results to Minami et al. (Minami et al., 2016).

In the analysis of macular thickness by using OCT, the mean value on pre-injection was 403.3 and the mean of day 45 was 339.4. which showed a statistically significant reduction in the macular thickness. These correlate with the study conducted by Sameera et al. (Sameera et al., 2016).

The mean IOP at day 1 was 16.56 and at day 7 was 14.68. whereas the mean pre-injection and at day 7 did not significantly change. This result was similar to earlier studies. (Yumusak et al., 2016). The AS examination showed that on the day of injection, 26 patients developed suprachoroidal haemorrhage (SCH), but on day 7, 0 patients developed SCH because it is a self-limiting condition.

Collectively in this study, changes in macular thickness by OCT and improved visual functions by BCVA are noted after single-dose razumab treatment from the pre-injection to 45 days shown in Figure 1 and Figure 2.

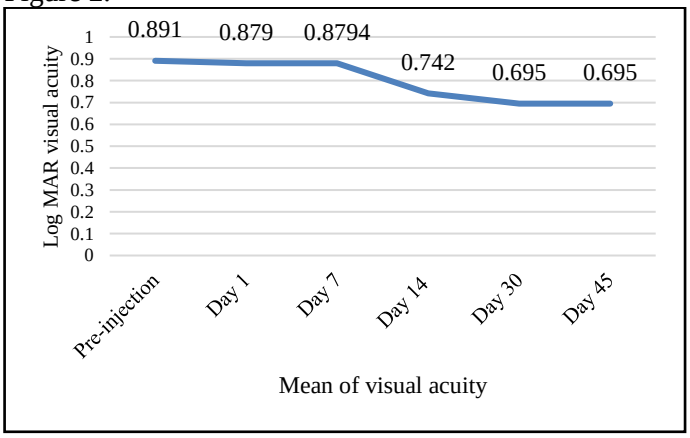

Figure 1. Visual acuity assessment – Mean improvement

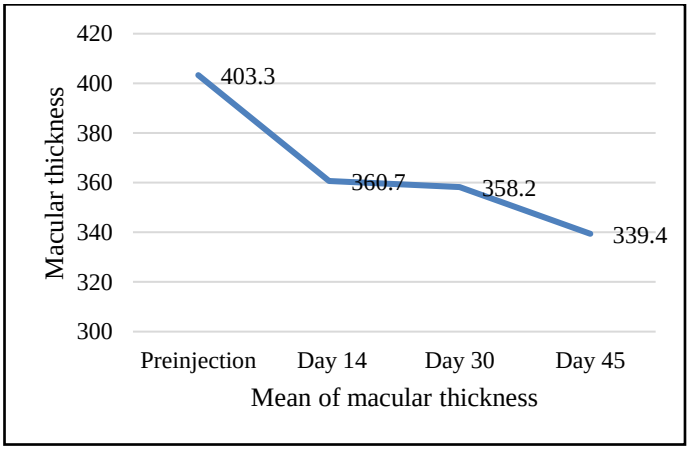

Figure 2. Macular thickness measurement – Mean reduction

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Table 2. Analysis of studied eyes according to log MAR best-corrected visual acuity

Row labels	LOG MAR BEST-CORRECTED VISUAL ACUITY					
	Pre-injection	Post-injection				
		Day 1	Day 7	Day 14	Day 30	Day 45
Min-Max	0.47-1.17	0.47-1.17	0.47-1.17	0.17-1.07	0.17-1.07	0.17-1.07
Mean ± SD	0.891± 0.195	0.879 ±0.199	0.8794± 0.199	0.742± 0.211	0.695± 0.217	0.695 ±0.217
Median	1	1	1	0.77	0.77	0.77
% of improvement	-	1.41%	-0.02%	15.31%	21.22%	21.22%
p-value						**<0.001*** **
significant at p≤0.05*, highly significant at p≤0.01*, very highly significant at p≤0.001***						

Table 3. Analysis of studied eyes according to the macular thickness (µm)

Row labels	MACULAR THICKNESS			
	Pre-injection	Post-injection		
		Day 14	Day 30	Day 45
Min-Max	298-721 µm	266-685 µm	240-650 µm	222-611 µm
Mean ± SD	403.3 ± 88.59	360.7 ± 87.78	358.2 ± 87.41	339.4 ± 85.93
Median	391.5	344	325	322
% of Improvement	-	4.49%	11%	15.7%
p-value				**<0.001*** **
significant at p≤0.05*, highly significant at p≤0.01**, very highly significant at p≤0.001***				

Table 4. Analysis of studied eyes based on IOP mmHg

Row labels	IOP		
	Pre- injection	Post-injection	
		Day 1	Day 7
Min-Max	12-20 mmHg	12-24 mmHg	11-19 mmHg
Mean ± SD	15.84 ± 2.427	16.56 ± 3.156	14.68 ± 2.113
Median	16	16	14.5
p-value			**<0.001*** **
significant at p≤0.05*, highly significant at p≤0.01**, very highly significant at p≤0.001***			

Table 5. Analysis of studied eyes based on Anterior segment examination

Row labels	A.S EXAMINATION		Total	Percentage
	No. of patients			
	SCH	No SCH		
Day 1	26	24	50	52%
Day 7	0	50	50	100%

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The effect of Razumab in the treatment of DME by increasing visual function and reducing macular thickness has been established in several studies((Browning et al., 2018; Campochiaro et al., 2010; Nguyen et al., 2010; Suñer et al., 2013). It not only improved visual function and reduced macular thickness, but it also prevented vision loss.

Conclusion

From this study, it may be concluded that a single-dose biosimilar Razumab injection was effective in the treatment of diabetic macular edema by improving visual acuity and reducing the macular thickness without causing any ocular concerns. Further studies are needed to investigate the long-term effectiveness of biosimilar Razumab injection in DME.

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