Visual Outcomes Following Intravitreal Ranibizumab for Diabetic Macular Edema in a Pro Re Nata Protocol from Baseline: A Real-World Experience

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Purpose: To investigate long-term outcomes of pro re nata (PRN) treatment protocol of ranibizumab for diabetic macular edema (DME) adopted from the first month of therapy without 3 loading doses.

Design: Retrospective interventional study.

Methods: We analyzed 180 eyes of 144 patients treated with ranibizumab for DME with a minimum follow-up of 1 year during December 2013 to December 2017. Data of all patients with treatment-naive center-involving DME who received at least 1 intravitreal injection of ranibizumab during the study period were drawn from a locally adapted electronic form for DME. The primary outcome measure was change in best-corrected visual acuity (BCVA) from baseline at 1-year follow-up, with intergroup comparisons in BCVA between eyes receiving 1, 2, and 3 injections in the first 3 months of treatment.

Results: The mean baseline BCVA was 0.47 ± 0.30 logMAR, which improved to 0.38 ± 0.3 logMAR (P = 0.003) at 3 months and stabilized at 0.35 ± 0.27 logMAR at 1 year (P = 0.46 vs BCVA at 3 months) and 0.34 ± 0.26 logMAR at 2 years of follow-up (P = 0.44 vs BCVA at 3 months). At 3 months, 24 eyes (13%) underwent 1 intravitreal injection, 52 eyes (29%) had 2 injections, and the majority (n = 104 eyes, 58%) had 3 injections on a monthly basis. During the first year, the group that received only 1 injection in the first 3 months also required fewer injections and fewer follow-up visits compared with those receiving 2 or 3 injections in the first 3 months.

Conclusions: One-third of eyes with DME responded well to PRN treatment strategy from the first month without 3 loading doses of ranibizumab. Baseline visual acuity is the best predictor of vision at 1 and 2 years of follow-up.

Key Words: anti-VEGF, diabetic macular edema, intravitreal injection, ranibizumab

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The incidence of diabetes mellitus (DM) is on the rise and has assumed pandemic proportions over the last 2 decades.[1,2] The prevalence of diabetic retinopathy (DR) is proportionally increasing, with latest studies showing that the overall prevalence may be as high as 35% for any DR, 7% for proliferative DR, and approximately 7% for diabetic macular edema (DME).[3–5]

Macular edema leads to moderate visual loss and affects quality of life.[6–8] Recent multicentric randomized clinical trials have established the role of intravitreal anti–vascular endothelial growth factor (anti-VEGF) agents in treating center-involving DME with visual loss.[9–12] Almost all the studies recommend a loading dose of anti-VEGF injections followed by a pro re nata (PRN) protocol. Real-world studies have reported similar or slightly inferior results to clinical trial results in terms of vision gain and improvements in central foveal thickness (CFT).[13–16] However, a majority of the real-world studies show that most physicians adopt an initial loading dose of at least 3 injections of anti-VEGF such as ranibizumab, followed by a PRN re-treatment protocol that is either based primarily on vision or optical coherence tomography (OCT)–based features. These strategies have been successful in reducing the number of injections for patients, yet cannot reduce the burden of repeated clinic visits over prolonged periods of time, contributing to significant patient loss to follow-up. To reduce the number of visits and yet maintain visual gains, the treat-and-extend regimen, an established approach for neovascular macular degeneration, has been suggested for the management of DME as well.[17]

There have been very few studies evaluating the effectiveness of treating DME with anti-VEGF and adopting a PRN regimen from the first month itself. While it is possible that some eyes may do well without the 3 loading doses, this concept has not been explored enough. Similarly, the cost of treatment may also be less if a proportion of eyes do not need the loading doses and yet maintain good vision over the long term. We conducted a retrospective study to understand what proportion of eyes do well without the 3 loading doses, how these eyes differ from those requiring the loading dose, and the long-term outcomes of PRN treatment protocol for DME when adopted from the very first month of initiation of anti-VEGF therapy.

METHODS

The study was approved by the local institutional review board and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients before initiation of intravitreal pharmacotherapy. Only data from those patients who had consented to anonymized data collection and analysis of outcomes as part of their clinical care were included in the study.

This was a retrospective interventional study of patients with unilateral or bilateral DME secondary to type 1 or type 2 DM visiting our department between December 2013 and December 2017. Case records of all patients with treatment-naive center-

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involving DME who received at least 1 intravitreal injection of ranibizumab during the study period were drawn from a locally adapted electronic form for DME. Data from patients older than 18 years with CFT of more than 400 μm and with a minimum follow-up of 1 year were included for analysis. Eyes with any prior intravitreal pharmacotherapy, significant cataract, vitreous surgery, and other conditions that may influence visual acuity such as corneal opacity, glaucoma, macular degeneration, retinal vein occlusion, and other retinal pathologies were excluded from the study.

At the time of presentation, patients underwent comprehensive ophthalmic evaluation including best-corrected visual acuity (BCVA) assessment using Early Treatment Diabetic Retinopathy Study (ETDRS) charts at 4 m (logMAR), intraocular pressure assessment using applanation tonometry, and dilated fundus examination using slit-lamp biomicroscopy to determine the presence of DME and grade of retinopathy. Macular OCT evaluation to determine the CFT was done with the Cirrus-HD 5000 (Carl Zeiss Meditec, Dublin, US) using the macular cube protocol. Baseline characteristics included for analysis were age, sex, eye involved, duration of DM, hemoglobin A_{1c} (HbA_{1c}) prior to starting ranibizumab, previous laser treatment, baseline BCVA in logMAR, and CFT. Once intravitreal ranibizumab was initiated, a PRN regimen was followed from the first month of follow-up. Our criteria for re-injection were persistence of intra-retinal fluid or worsening of diabetic maculopathy on OCT scan. Re-injection was withheld if visual acuity was 0.0 and absence of intra-retinal fluid, or if BCVA and OCT were stable for 2 consecutive visits. If worsening of BCVA (>5 letter loss) or OCT (increase >10%) was noticed at follow-up, reinjection was given. At each visit, patients underwent visual acuity assessment and OCT for macular assessment as mentioned above. Monthly follow-up visits were scheduled based on BCVA and OCT thickness at the current visit. If the eye condition was assessed as stable, patients were advised to follow-up after 2 months, with provision of earlier follow-up if they noticed any subjective drop or change in vision. The maximum interval allowed between follow-up visits was 3 months.

The BCVA at baseline was measured in logarithm of minimum angle of resolution (logMAR). Visual acuity (logMAR) and CFT measured at 1 month, 3 months, 1 year, and 2 years were collected for statistical analysis. The number of injections and the total number of visits at 3 months, 1 year, and 2 years during the study were also recorded for analysis.

Outcome Measures

The primary outcome measure was change in BCVA from baseline at 1-year follow-up, with intergroup comparisons in BCVA between eyes receiving 1, 2, and 3 injections in the first 3 months of treatment initiation. The secondary outcome measures were the change in BCVA at 2 years and change in CFT across the 3 groups.

Statistical Analyses

Continuous data were presented as mean ± SD or median with interquartile range (IQR) and categorical variables were expressed as proportions. Comparisons between pre- and post-treatment at various times points were assessed using the paired *t* test.

Group differences in continuous variables across the 2 groups were analyzed using student *t* test or Wilcoxon rank sum test for non-parametric data. Differences across 3 groups were

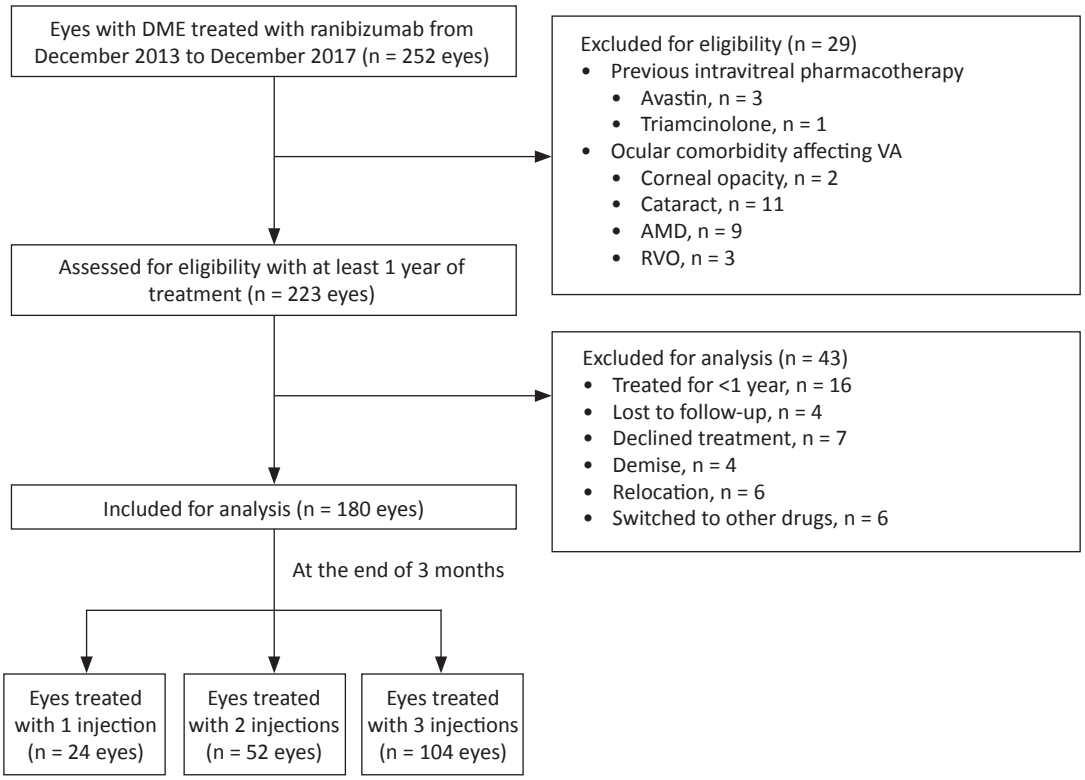

FIGURE 1. Flowchart of the study patients. AMD indicates age-related macular degeneration; DME, diabetic macular edema; RVO, retinal vein occlusion; VA, visual acuity.

analyzed using analysis of variance or Kruskal-Wallis test for data with non-parametric distribution. Group differences between categorical variables were analyzed using the chi-square or Fisher exact test.

Factors influencing BCVA at various time points were analyzed using univariate and multivariable linear regression analysis. Covariates for regression models were chosen from those that showed significance in univariate models ($P < 0.1$) or those that had clinical relevance. Correlation between BCVA at baseline and at various time points was assessed using Pearson correlation coefficient and was graphically presented using Locally Weighted Scatterplot Smoothing (LOWESS) curves.

All data were entered in Excel (Microsoft Excel for windows, 2017) and analyzed using STATA 12.1 I/c (StataCorp, Fort Worth, Texas, US). All *P* values less than 0.05 were considered statistically significant, except those used in multivariate analysis ($P < 0.1$).

RESULTS

A total of 252 eyes received ranibizumab for DME during the study period. We excluded 72 eyes from analysis for reasons such as previous pharmacotherapy, other ocular comorbidity affecting visual acuity, lost to follow-up, declined treatment, or relocation. As a result, 180 eyes of 144 patients were included (Fig. 1). The mean (± SD) age of patients was 66.9 ± 13.2 years (median, 66.5 years; IQR, 58–76 years; range, 26–101 years) and 85 (59%) were men. The mean duration of DM in the study cohort was 15.6 ± 10.1 years (median, 15 years; IQR, 8–20 years) and the majority were type 2 DM (n = 134, 93%). The mean HbA_{1c} at the time of first consultation was 8.3% ± 1.7% and the mean triglyceride level was 1.66 ± 0.9 mmol/L. Fifty-eight eyes (32%) had mild non-proliferative diabetic retinopathy (NPDR), 53 eyes (29%) had moderate NPDR, 24 (13%) eyes had severe NPDR, and 45 eyes (25%) had proliferative DR. Adjuvant laser treatment was done in 15 patients and none received supplementary steroid

TABLE 1. Comparison of demographic and clinical characteristics at various time points in eyes requiring 1, 2, and 3 injections in the first 3 months*

Characteristic	1 Injection (n = 24)	2 Injections (n = 52)	3 Injections (n = 104)	*P* Value
Baseline				
Age, y	63.6 ± 19	67.3 ± 19	67.5 ± 19	0.82
Sex (men)	11 (46%)	26 (50%)	48 (46%)	0.91
DM duration, y	16.5 ± 9.5	17.3 ± 10.4	14.5 ± 10.1	0.11
HbA_{1c} at baseline, %	8.4 ± 1.5	8.2 ± 1.7	8.3 ± 1.7	0.74
TG at baseline, mmol/L	1.61 ± 0.6	1.84 ± 1.2	1.57 ± 0.8	0.42
BCVA (logMAR)	0.33 ± 0.2	0.47 ± 0.3	0.51 ± 0.3	0.03
CFT, µm	459 ± 58	449 ± 64	464 ± 78	0.46
No. received macular laser	17 (71%)	39 (76%)	76 (73%)	0.85
DR grade				0.79
Mild NPDR	8 (33%)	20 (38%)	30 (29%)	
Moderate NPDR	8 (33%)	12 (23%)	33 (32%)	
Severe NPDR	4 (17%)	6 (11%)	14 (13%)	
PDR	4 (17%)	14 (27%)	27 (26%)	
At 1 month				
BCVA (logMAR)	0.22 ± 0.15	0.38 ± 0.27	0.45 ± 0.29	0.01
CFT, µm	317 ± 66	340 ± 60	386 ± 73	<0.001
At 3 months				
BCVA (logMAR)	0.29 ± 0.3	0.33 ± 0.3	0.43 ± 0.3	0.05
CFT, µm	331 ± 79	320 ± 70	349 ± 92	0.16
At 1 year				
BCVA (logMAR)	0.24 ± 0.2	0.37 ± 0.3	0.42 ± 0.3	0.03
2 Line gainers (n, %)	7 (29%)	20 (38%)	36 (35%)	0.73
2 Line losers (n, %)	3 (12%)	5 (10%)	15 (14%)	0.70
CFT, µm	340 ± 95	346 ± 86	346 ± 97	0.89
No. of injections	4 ± 2.9	4.6 ± 2.3	5.9 ± 2.1	0.001
No. of visits	9 ± 3	10 ± 3	10 ± 3	0.06
At 2 years	(n = 13)	(n = 42)	(n = 77)	
BCVA (logMAR)	0.18 ± 0.2	0.3 ± 0.2	0.38 ± 0.3	0.02
CFT, µm	317 ± 98	308 ± 63	335 ± 97	0.51
No. of injections	2 ± 2.2	2.6 ± 2.2	2.6 ± 2.9	0.54
No. of visits	6.6 ± 2.9	8.0 ± 3.1	7.8 ± 2.5	0.25

BCVA indicates best-corrected visual acuity; CFT, central foveal thickness; DM, diabetes mellitus; DR, diabetic retinopathy; HbA_{1c}, hemoglobin A_{1c}; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; TG, triglycerides.

* Data are shown in mean ± SD or No. (%), unless otherwise stated.

injection.

The mean baseline BCVA was 0.47 ± 0.30 logMAR, which improved to 0.38 ± 0.3 logMAR (P = 0.003) at 3 months with a median of 3 injections (IQR, 2–3 injections). Thereafter, the BCVA stabilized at 0.35 ± 0.27 logMAR at 1 year (P = 0.46 vs BCVA at 3 months) with a median of 5 injections (IQR, 4–7 injections) and 0.34 ± 0.26 logMAR at 2 years of follow-up (P = 0.44 vs BCVA at 3 months) with a median of 2 injections (IQR, 0–4 injections). The mean baseline CFT was 459 ± 72 µm which reduced to 339 ± 85 µm at 3 months. The CFT was stable at 12 months' follow-up (mean, 344 ± 95 µm, P = 0.32) and reduced further to 325 ± 88 µm at 2 years' follow up. The mean number of follow-up visits at 12 months was 10.4 ± 2.6 (median, 10; IQR, 9–12; range, 4–18 visits) and mean number of visits between year 1 and 2 was 7.8 ± 2.7 (median, 8; IQR, 6–10 visits).

At 3 months, 24 eyes (13%) underwent 1 intravitreal injection, 52 eyes (29%) had 2 injections, and the majority (104 eyes, 58%) had 3 injections on a monthly basis. Table 1 shows the comparison of the baseline and follow-up characteristics of those requiring 1, 2, and 3 injections up to 3 months. Those given only 1 injection had significantly better BCVA at baseline compared with those who were given more injections. This trend continued consistently at all time points till 24 months of follow-up period (Fig. 2). During the first year, this group also required fewer injections and fewer follow-up visits compared with those who received 2 or 3 injections in the first 3 months. There were no intergroup differences in eyes that gained or lost 10 letters on the ETDRS chart. The CFT was similar across these groups at every time point except that at 1 month (Fig. 3). Between year 1 and 2, there was no difference in the number of injections required and follow-up visits with all eyes requiring approximately 2 to 3 injections. Figure 4 shows a strong correlation between BCVA at baseline and at 1 year across eyes that required 1, 2, and 3 injections in the first 3 months (correlation coefficient = 0.72, P < 0.001).

Univariate and multivariable linear regression showed that lower BCVA at baseline was predictive of lower BCVA at every time point, even after adjusting for CFT and number of injections (Table 2). Additionally, greater CFT at baseline was associated with lower BCVA at 1 and 2 years of follow-up.

DISCUSSION

We found that eyes with DME do well and maintain relatively good visual acuity at 1 and 2 years of follow-up using a PRN retreatment protocol from the very first month. Importantly, we identified subgroups of patients who did equally well without 3 loading doses, although there was an absence of a control group matching this subgroup of patients. More than one-third of the eyes in our study did not require a monthly loading dose at the

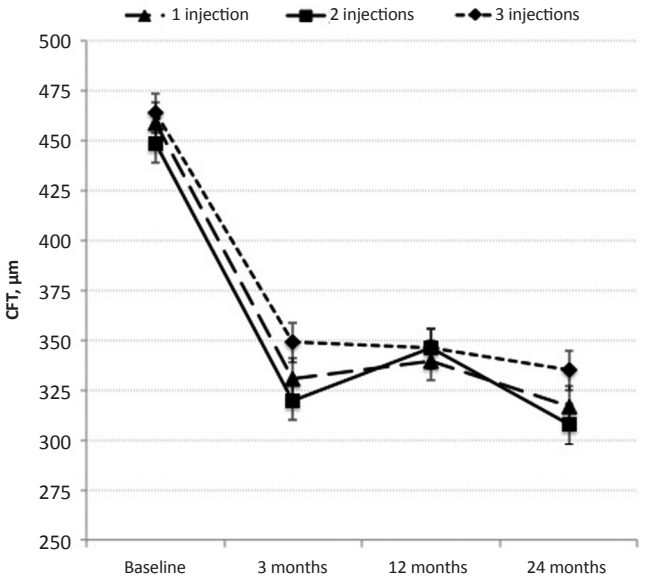

FIGURE 3. Comparison of central foveal thickness (CFT) at different time points in eyes requiring 1, 2, and 3 intravitreal ranibizumab injections on a monthly basis in the first 3 months of treatment. Error bars indicate 95% confidence intervals.

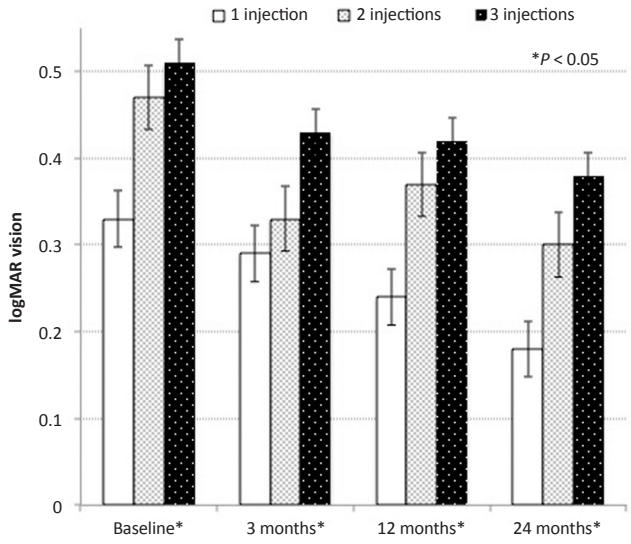

FIGURE 2. Comparison of visual acuity at different time points in eyes requiring 1, 2, and 3 intravitreal ranibizumab injections on a monthly basis in the first 3 months of treatment. Error bars indicate 95% confidence intervals.

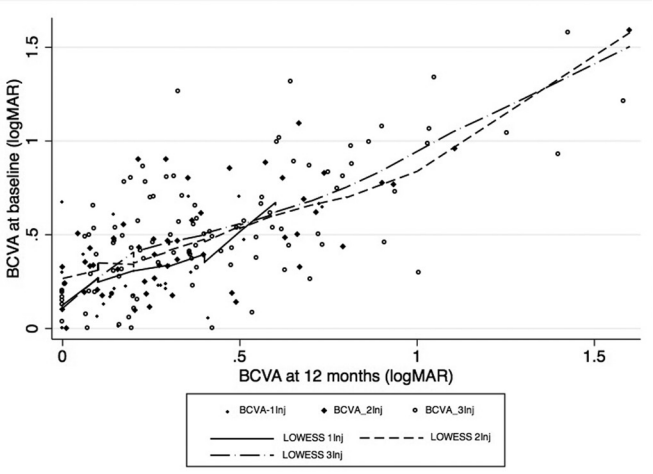

FIGURE 4. LOWESS curve showing correlation between best-corrected visual acuity (BCVA) at baseline and 1 year across eyes that required 1, 2, and 3 injections on a monthly basis in the first 3 months of treatment.

TABLE 2. Univariate and multivariable linear regression analysis to determine factors predictive of vision at each time point

		Univariate Analysis			Multivariable Analysis		
Predictors of Vision	**Interval**	**B Coeff**	**95% CI**	***P* Value**	**B Coeff**	**95% CI**	***P* Value**
At 3 months							
Age	1 year increment	0.004	0 to 0.007	0.015	0.003	0 to 0.005	0.04
BCVA at baseline	0.1 logMAR increment	0.34	0.21 to 0.48	<0.001	0.31	0.16 to 0.45	<0.001
CFT at baseline	100 μm increment	0.03	0 to 0.09	0.24	−0.004	0 to 0.005	0.88
CFT at 3 months	100 μm increment	0.04	0 to 0.09	0.10	-	-	-
No. of injections	2 vs 1 injection	0.03	−0.1 to 0.1	0.6	−0.01	−0.15 to 0.1	0.84
	3 vs 1 injection	0.13	0 to 0.26	0.05	0.06	−0.06 to 0.2	0.31
DR grade	vs mild NPDR	0.02	−0.01 to 0.06	0.17	0.03	−0.01 to 0.06	0.15
HbA_{1c}	0.1% increment	0.03	0 to 0.05	0.09	0.02	-0.01 to 0.05	0.06
TG	10 units increment	−0.015	−0.06 to 0.03	0.52	-	-	-
At 1 year							
BCVA at baseline	0.1 logMAR increment	0.73	0.63 to 0.83	<0.001	0.69	0.62 to 0.83	<0.001
CFT at baseline	100 μm increment	0.14	0.08 to 0.20	<0.001	0.05	0.03 to 0.9	<0.001
No. of injections	Per 1 injection increment	−0.002	−0.002 to 0.02	0.78	−0.007	−0.02 to 0.005	0.55
At 2 years							
BCVA at baseline	0.1 logMAR increment	0.62	0.49 to 0.74	<0.001	0.62	0.51 to 0.73	<0.001
CFT at baseline	100 μm increment	0.05	0.04 to 0.1	0.08	0.06	0.02 to 0.1	0.02
No. of injections	Per 1 injection increment	0.009	−0.008 to 0.02	0.31	0.005	−0.007 to 0.02	0.43

BCVA indicates best-corrected visual acuity; CFT, central foveal thickness; CI, confidence interval; DR, diabetic retinopathy; HbA_{1c}, hemoglobin A_{1c}; NPDR, non-proliferative diabetic retinopathy; TG, triglycerides.

initiation of intravitreal ranibizumab. These eyes had slightly better vision at baseline (0.1) and continued to have significantly better vision at 1 year with fewer injections and fewer follow-up visits. Baseline vision was found to be the best predictor of vision at 1 and 2 years of follow-up in the regression models.

In a retrospective study similar to ours, Ebneter et al[13] compared outcomes of PRN injections based on BCVA versus OCT-based treat-and-extend regimen for the treatment of DME. In the BCVA-based PRN arm, authors reported a mean gain in the vision of 8.3 ETDRS letters at 12 months of follow-up with a mean of 6 injections. In our study, the cohort of eyes that received only 1 injection within the first 3 months showed a 10-letter gain at 12 months with a mean of 4 injections, similar to the results shown by Ebneter et al.[13] At 2 years, with about 50% eyes from this group being followed up, the mean BCVA was 0.2 with about 7 injections in total. Approximately one-third of the eyes in our study required only 2 injections in the first 3 months, and these eyes also showed a 5-letter gain at 1 year with a mean of 5 injections. At 2 years, these eyes retained a mean vision of 0.3 with a mean of 10 injections. Hence it appears that there is a significant cohort of eyes that retain good vision as well as require fewer injections over 2 years, despite not receiving the recommended 3 loading doses in the first 3 months. This may be because the VEGF levels in DME are influenced by the systemic status and wax and wane after the onset of edema. It is difficult to obtain serial in vivo VEGF levels from human eyes. However, the fluctuating levels of VEGF in DME may explain the need for fewer anti-VEGF injections in about a third of these eyes. It is presumed that the VEGF load is much higher in eyes with vein occlusions compared with DME and neovascular age-related macular degeneration.[18] Although monthly anti-VEFG injections followed by treat-and-extend strategies are probably the best way to get optimum results in vein occlusions and neovascular age-related macular degeneration, DME may be amenable to treatment with PRN right from the beginning. Our finding puts forward the need for a randomized controlled trial for the same in future.

The third cohort in our study comprising 59% of the eyes analyzed received 3 loading doses of ranibizumab followed by PRN injections based primarily on vision. This group showed a visual gain of 7 letters with 9 injections in the first year and an additional 3 injections in the second year. The results are similar to the PRN ranibizumab arm of the RETAIN study which showed a 7-letter gain with a median of 10 injections at 2 years.[17] Our re-treatment criteria were similar to those used for the RETAIN study and were modeled on the landmark RESTORE study.[9] The ranibizumab + sham group of the RESTORE study was very similar to this cohort at baseline and showed a mean gain of 5 letters with a median of 7 injections at 1 year. The main difference between these multicentric randomized studies and ours was that our study was retrospective, and a PRN regimen was applied from the first month itself, rather than after 3-monthly loading doses.

Baseline visual acuity was found to be the best and strongest predictor of vision at 1 and 2 years of follow-up, irrespective of the number of injections used. The CFT at these time points also influenced vision, however the magnitude of impact was negligible compared with vision at presentation. This could possibly be explained by the amount of macular ischemia as it has a negative impact on the visual outcome and does not affect the anatomical outcome.[19] Combining data from 9 clinical trials, Dugel et al[20] have shown that eyes with lower BCVA at baseline tended to gain greater lines during these studies. Good baseline vision may be associated with better structural and functional integrity of the inner plexiform layer and hence eyes with good

BCVA at baseline had the best outcomes at 1 and 2 years of follow-up in our study. Interestingly macular ischemia has a negative impact on the visual outcome but has no influence on the anatomical outcome.

There may be considerable reduction in health care costs if a third of the patients do not receive the 3 loading doses for treating DME, as recommended in this study. A sustained need for fewer injections and fewer follow-up visits over 1 year in this cohort makes it important to tease out these eyes at baseline. In resource-poor settings, especially in the developing world, a PRN strategy adopted right from the first month may be a good option for treating DME with good outcomes. A head-to-head comparative study with formal cost-effectiveness analysis is required to establish whether PRN from the first month is as good as PRN after 3 loading doses in terms of visual outcomes and costs.

The limitations of this study included its retrospective nature and lack of structural characteristics on OCT, as well as the absence of a control group matching those subgroups of patients. However, the relatively large sample size from a single center with serial measurement of clinical parameters over 1 and 2 years, and the use of standard retreatment and follow-up criteria were the strengths of this study.

In conclusion, about a third of eyes with DME responded well with excellent visual and anatomical outcomes using PRN treatment strategy from the first month without 3 loading doses of ranibizumab. These eyes require fewer injections and follow-up visits compared with those who require 3 loading doses. Baseline visual acuity is the best predictor of vision at 1 and 2 years of follow-up. Adopting PRN treatment protocols right from the first month is an effective and perhaps an economical way of treating DME and may be recommended in resource-poor settings if validated in a randomized controlled trial.

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