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ORIGINAL PAPER

Real-life experience of ranibizumab for diabetic macular edema in Taiwan

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Abstract

Purpose To evaluate the visual and anatomical outcomes of intravitreal ranibizumab for diabetic macular edema (DME) in the healthcare system of Taiwan.

Methods A total of 39 eyes from 39 patients were retrospectively enrolled in the study. All eyes that fulfilled the key criteria, including a baseline vision between 20 and 70 ETDRS letters and a minimum central macular thickness (CMT) of 300 μm, had at least 3 monthly loading injections of ranibizumab in a year. Macular laser or posterior subtenon injections of triamcinolone acetonide (PSTA) could be performed as supplementary treatments following loading injections. Primary outcomes include best-corrected visual acuity and CMT.

Results Patients' vision improved from 46.5 ± 15.3 letters at baseline to 51.4 ± 16.6 letters at 12 months ($p = 0.031$). Mean CMT at baseline was 406 ± 105 μm, which decreased to 329 ± 108 μm ($p = 0.002$). At 12 months, 44.4% of eyes with total injection number < 5 and 42.9% with injection number ≥ 5 achieved a gain in vision that was 10 letters or more. A total of 5 injections or more did not lead to a better visual gain in comparison with only 3–4 injections ($p = 0.71$), and both had similar number of supplementary treatments ($p = 0.43$). Monthly reinjections of ranibizumab resulted in a lower likelihood of visual loss of 10 or 15 letters ($p = 0.019$ and 0.015, respectively, adjusted for age, baseline vision, severity of diabetic retinopathy and the presence of previous treatments); however, supplementary macular lasers, PSTA or ranibizumab without monthly reinjections did not (all $p > 0.05$). The average number of injections was 4.3 ± 1.0.

Conclusion Treatment for DME with at least three monthly ranibizumab loading injections, with or without other supplementary treatments, is effective at 12 months thereafter. Two monthly reinjections of ranibizumab, while not significantly increasing vision, may have a role in preventing visual loss.

Keywords Diabetic macular edema · Intravitreal injections · Ranibizumab · Best-corrected visual acuity

Abbreviations

DME Diabetic macular edema

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VEGF	Vascular endothelial growth factor
ETDRS	Early Treatment Diabetic Retinopathy Study
BCVA	Best-corrected visual acuity
CMT	Central macular thickness
PSTA	Posterior subtenon injection of triamcinolone acetonide

Introduction

Diabetic macular edema is one of the most well-known vision-threatening complications of diabetes mellitus. It is also a major cause of visual loss worldwide, with an estimated prevalence of 7.5% in diabetic patients [1, 2]. That figure may continue to rise in aging populations. Risk factors for diabetic retinopathy and DME include sustained hyperglycemia, hypertension, dyslipidemia, systemic inflammatory disorders and various genetic factors. The pathogenesis for DME has been extensively investigated; advanced glycation end products resulting from sustained hyperglycemia produce oxidative stress and damage on retinal microvasculature [3, 4]. The upregulation of vascular endothelial growth factors (VEGF) and inflammatory cytokines further leads to the breakdown of blood retinal barrier and capillary leakage [1, 4]. Pharmaceutical treatments are largely based on considerations of these biochemical mechanisms, including a number of anti-VEGF agents such as triamcinolone acetonide injections and dexamethasone implants [5–7]. Macular laser alone has achieved lower efficacy and may have an ancillary role in the era of anti-VEGF treatment [8, 9].

Ranibizumab is a humanized monoclonal antibody fragment that targets VEGF, and has been approved in many countries for the treatment for DME. Intravitreal injection of ranibizumab is safe and leads to substantial improvement in vision, with a gain ranging from 6.5 to 10.3 ETDRS letters, depending on varying protocols and treatment exposures [8–13]. Previous Asian studies have reported that the average number of injections needed was 7.0 for 12 months [8, 13].

Despite the excellent outcomes, multiple injections are usually required. The cost of such injections has posed challenges for patients, physicians and policy makers [14]. In Taiwan, the expense of ranibizumab injections has been covered by reimbursements through the National Health Insurance. Before February 2016, a maximum of five injections can be applied for each eye for the first year. Patients who show evidence of improvement after three initial injections were allowed to obtain two further injections for the rest of the year. Beyond the coverage of the health insurance, patients also had the option to acquire ranibizumab injections at their own expense. Thus, our study is aimed at evaluating the outcomes at 1 year post-injections. We report on the real-world efficacy of Taiwanese patients who have undergone at least three monthly injections of ranibizumab during their first year and analyze the correlating factors for visual outcomes.

Materials and methods

Study population

We conducted a retrospective chart review from October 2012 to July 2016 of the Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei, Taiwan. Only one eye from each patient would be enrolled. All patients with DME had completed at least three consecutive monthly intravitreal injections of ranibizumab at 0.5 mg, with 1 year of follow-up. The cost of ranibizumab was reimbursed through the National Health Insurance, which also guided treatments and had the main inclusion criteria at baseline as follows: (1) best-corrected visual acuity ranging from 20/40 to 20/400, (2) macular edema evidenced by a CMT value of 300 μm or more as well as leakage shown by fluorescein angiography and (3) HbA1c level less than 10%. Patients who met the above criteria could apply for the first three injections. After the three loading injections of ranibizumab, those showing significant improvements could apply for two more injections, while the final permission for application was directly judged by reviewers from the National Health Insurance. The treatment protocol after the first three loading injections was based on the individualized results of the second application, as well as on the doctors' judgments. Macular laser or posterior subtenon injections of triamcinolone acetonide (PSTA) were ancillary to ranibizumab and could either be performed when reinjections were no longer available for persistent edema with residual intraretinal cyst or subretinal fluid during follow-up

after at least three loading injections. While laser was allowed to be performed based on ETDRS guidelines with a minimal interval of 90 days, the decisions to perform laser or PSTA were at the physicians' discretion. We excluded patients who underwent any previous pars plana vitrectomy or any intraocular surgery or injections with anti-VEGF within 3 months prior to the inclusion. In addition, patients with surgeries such as cataract extraction or pars plana vitrectomy during the study period were also excluded. Other key exclusion criteria included uncontrolled glaucoma under topical medications and macular edema due to other causes. This research adhered to the tenets of the Declaration of Helsinki, while institutional review board (IRB) approval was obtained from the IRB of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation.

Data collection

The values of Snellen visual acuity were transformed into ETDRS letters for statistical purposes. Central macular thickness was documented by OCT (Cirrus HD-OCT 400, Carl Zeiss Meditec, Dublin, CA, USA). Both vision and central macular thickness were documented at baseline, 3, 6 and 12 months thereafter.

Statistical analysis

Examinations for differences in best-corrected visual acuity (BCVA) and central macular thickness (CMT) between baseline and each follow-up session were performed through paired *t* tests with Bonferroni correction for multiple comparisons. Differences in both BCVA and CMT over the course of treatment between patients who received 5 or more ranibizumab injections and those who received less than 5 were examined through Mann–Whitney *U* test. Time intervals between the last two injections were categorized to correlate with final visual outcome by Spearman's partial correlations, while controlling for baseline factors including age, baseline BCVA, severity of diabetic retinopathy (non-proliferative vs. proliferative) and the presence of previous treatments. Retreatment factors for visual loss were also evaluated by Spearman's partial correlation. Baseline predictors for changes in vision after the loading phase were analyzed by multiple linear regression models. SPSS for Windows (version 18; SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. p values less than 0.05 were considered statistically significant.

Result

Baseline characteristics

A total of 39 eyes from 39 patients with a follow-up time of 1 year were enrolled in the study. The allocation process is shown in Fig. 1. The mean age of the sample was 61.7 ± 8.3 years (mean ± SD), while the mean HbA1c at the time of inclusion was 7.4 ± 1.5% (mean ± SD). Among the 39 eyes, 27 had proliferative diabetic retinopathy, and 21 of them had previous panretinal photocoagulation. Previous treatments for macular edema were observed in 11 eyes, including anti-VEGF agents in 8 eyes (20.5%), posterior subtenon injections of triamcinolone acetonide (PSTA) in 5 eyes (12.8%), and macular laser in 5 eyes (12.8%). Details are listed in Table 1. In these eyes, the median interval between the previous treatments and the first injection of ranibizumab was 19.9 weeks (range 13.9–106.9 weeks).

Treatment course and primary outcomes

Of the 39 eyes in this study, 21 (53.8%) received two additional injections of ranibizumab after the three initial loading injections, while 18 eyes (46.2%) received only one additional injection or less within a year. Among these 21 eyes that completed at least five injections as shown in Fig. 1, 19 eyes received a total of 5 injections over a 12-month period, and the other 2 eyes had 6 injections over a 12-month period. Also among these 21 eyes, seven of them (including 6 eyes with 5 injections and 1 eye with 6 injections) received their total injections within the first 6 months, while the rest of fourteen eyes (including 13 eyes with 5 injections and 1 eye with 6 injections) did not. The mean total number of ranibizumab injections of the 39 eyes was 4.3 ± 1.0. Between 3 and 12 months, PSTA was performed in eight eyes (20.5%), while macular laser was performed in four eyes (10.3%) as a supplementary treatment.

The BCVA improved significantly at 3 and 12 months compared with the baseline ($p < 0.001$ and $p = 0.031$, respectively), but not at 6 months ($p = 0.103$). As for central macular thickness, an

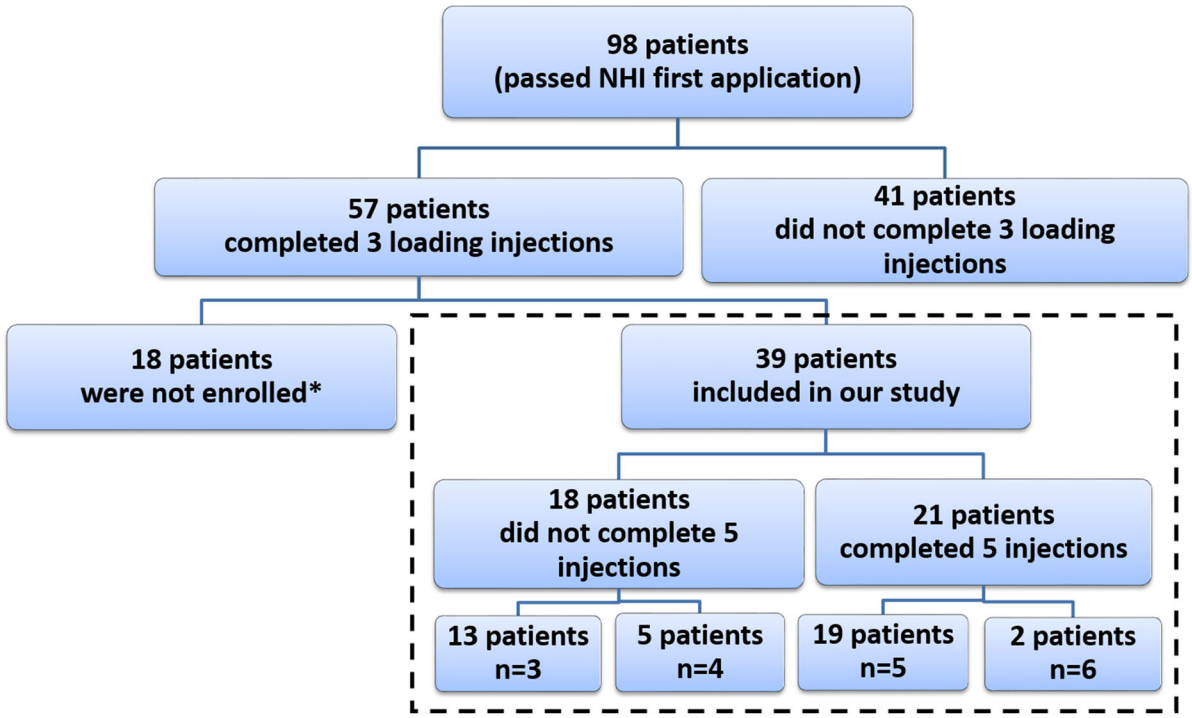

Fig. 1 Patient allocation process. The asterisk* denotes the 18 patients not enrolled in this study for statistical analysis due to the following reasons other than three loading injections, including 5 (5.1%) with previous pars plana vitrectomy or recent intraocular surgery prior to inclusion, 3 (3.1%) having cataract surgery during follow-up, 10 (10.2%) with incomplete documentation or follow-up. *NHI* National Health Insurance, *n*: total number of ranibizumab injections

Table 1 Patient demographic and baseline characteristics

Age (years, mean ± SD)	61.7 ± 8.3
HbA1c (%, mean ± SD)	7.4 ± 1.5
Systemic comorbidities, *n*(%)	
Insulin dependent	9 (23.1%)
Chronic renal failure	19 (48.7%)
Proliferative diabetic retinopathy, *n*(%)	27 (69.2%)
Previous PRP, *n*(%)	21 (53.8%)
Previous treatment for ME, *n*(%)	11 (28.2%)
Anti-VEGF agents	8 (20.5%)
PSTA	5 (12.8%)
Macular laser	5 (12.8%)

HbA1c glycosylated hemoglobin A1c, *ME* macular edema, *PRP* panretinal photocoagulation, *PSTA* posterior subtenon injection of triamcinolone acetonide

improvement was also observed at 3 months ($p < 0.001$), which was relatively maintained at 6 and 12 months ($p = 0.001$, $p = 0.002$, respectively, compared with the baseline). When further analyzed by the number of injections, both BCVA and CMT did not differ significantly between patients who received 5 injections or more and those who received less than 5 injections at any time point in a year (all $p > 0.05$). (See Fig. 2 and Table S1, S2 for exact number.)

Outcomes based on severity at baseline

Eyes with a baseline BCVA of less than 50 letters tended to have a greater visual gain compared with those with a baseline BCVA of 50 letters or more at 12 months (7.8 vs. 2.7 letters, respectively, $p = 0.24$). The change in central macular thickness was similar (− 68 vs. − 85 μm, respectively, $p = 0.53$) (Fig. 3a, b). Eyes with a baseline CMT of 400 μm or more tended to have greater visual gain than those with a baseline CMT of < 400 μm over the course of the follow-up, although the difference became smaller at 12 months (Fig. 3c). As for the anatomical outcome, eyes in both groups had their CMT reduced to similar levels after 3 loading injections; however, those with

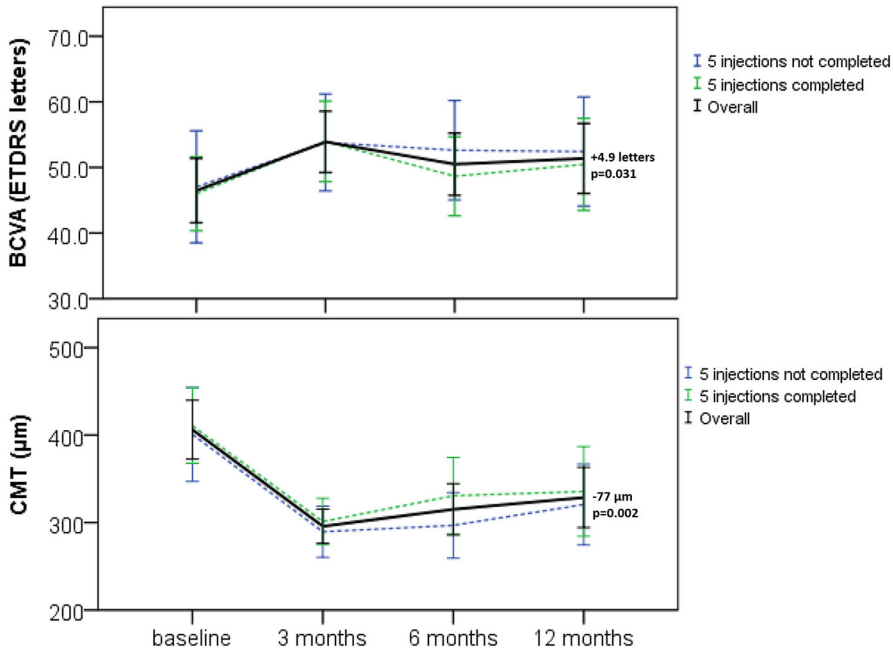

Fig. 2 Primary outcomes of best-corrected visual acuity (BCVA) and central macular thickness (CMT) over the course of treatment compared with baseline values. Both BCVA and CMT significantly improved at 12 months ($p = 0.031$ and $p = 0.002$, respectively, adjusted with Bonferroni method for multiple comparisons). The differences between those who received 5 injections or more ($n = 21$) and those who received less than 5 injections ($n = 18$) were not statistically significant at any time points (dashed lines, all $p > 0.05$). Data are shown in mean ± 2SE. (Also see Table S1, S2 for exact number)

greater CMT at baseline tended to rebound more at 12 months (Fig. 3d).

Analysis of time points for consecutive injections

The scatter plot (Fig. 4) shows the distribution of actual time points of treatment between the 3rd and 4th injection (upper panel) as well as the 4th and 5th injection (lower panel) in relation to final visual change from the baseline. The interval between 3rd and 4th injections was 14.5 ± 7.8 weeks (mean ± SD) and 6.7 ± 2.9 weeks between the 4th and 5th injections. The interval between 3rd and 4th injections was not associated with final visual outcome ($r = 0.135$, $p = 0.55$). Shorter intervals between 4th and 5th injections were correlated with better visual outcome at 12 months ($r = -0.536$, $p = 0.027$).

Analysis for completion of five total injections

The mean number of total ranibizumab injections in a year was 5.1 ± 0.3 in those with 5 or more injections and 3.3 ± 0.5 in those with less than 5 injections ($p < 0.001$, Mann–Whitney U test). Percentages of visual changes are shown in Table 2. Both changes in vision and macular thickness at 12 months were not significantly associated with the completion of 5 injections ($r = -0.032$, $p = 0.857$, and $r = 0.097$, $p = 0.579$, respectively, after adjustment for age, baseline BCVA, severity of diabetic retinopathy and the presence of previous treatment; Spearman's partial correlation). For eyes that were treated with consecutive 4th and 5th monthly injections, the initiation of reinjections before 6 months tended to have more letters gained, as well as reduced macular thickness. At 12 months, the average visual gain was 9.0 letters in the subgroup within 6 months and 5.5 letters in the subgroup beyond (Table 3).

Previous treatment and change of visual acuity after loading phase

Baseline vision was 50.7 ± 13.8 letters in the previously treated group, compared with 44.8 ± 15.8 letters in the treatment naïve group. Subgroup analysis in previously treated eyes showed 51.0 ± 16.5 letters

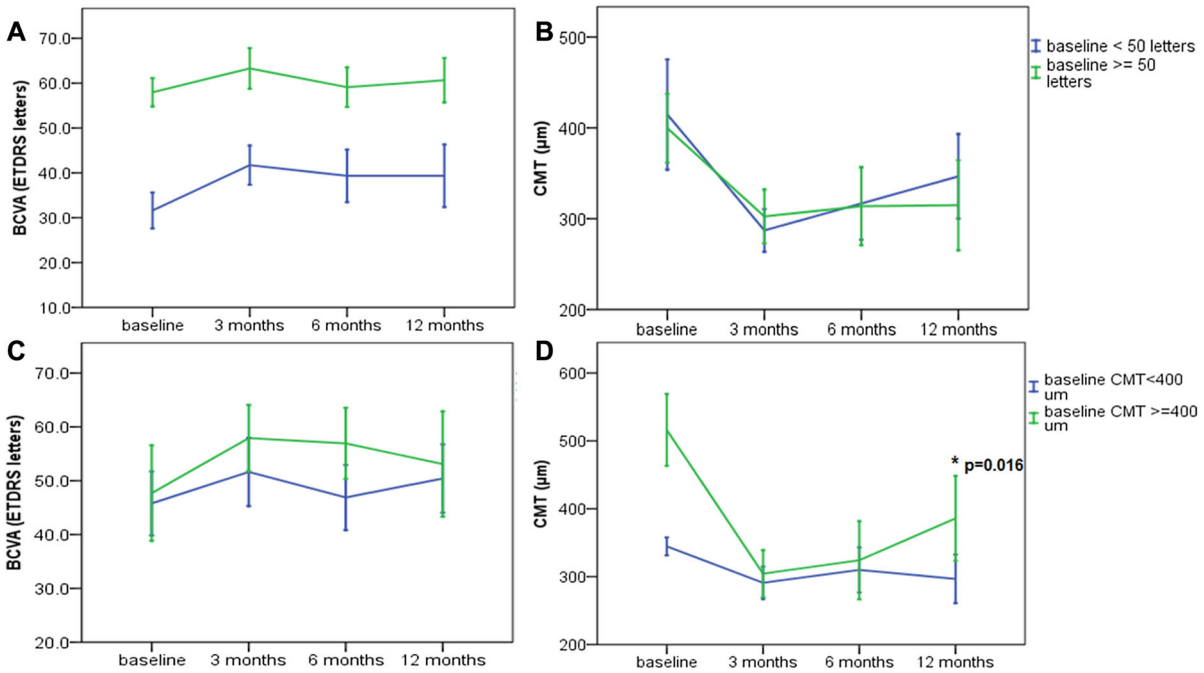

Fig. 3 Outcomes of best-corrected visual acuity and central macular thickness according to different baseline severity. **a**, **b** Present eyes with baseline BCVA < 50 letters (n = 18) or ≥ 50 letters (n = 21), respectively, while **c**, **d** present eyes with baseline thickness ≥ 400 μm (n = 14) or < 400 μm (n = 25), respectively. Eyes with baseline thickness ≥ 400 μm tended to rebound at 12 months compared with those with thickness < 400 μm (p = 0.016, Mann–Whitney U test). Data are shown in mean ± 2SE

in the anti-VEGF group, 55.8 ± 8.8 letters in PSTA and 45.8 ± 15.0 letters in those who have undergone macular laser. Among these eyes, there were no differences in vision at any time points between eyes previously treated with only one type (n = 5) and those with combination of any of these regimens (n = 6) (all $p > 0.05$, Mann–Whitney U test). Better baseline vision predicted lower visual gain at 3 months. Age, severity of diabetic retinopathy and previous treatment modalities did not have significant effects on visual changes (Table 4).

Retreatment with PSTA, macular laser or ranibizumab

Eyes receiving PSTA or macular lasers after 3 loading injections (n = 12) had worse vision at baseline (41.9 ± 18.1 vs. 48.5 ± 13.8 letters). The presence of these supplementary treatments did not differ significantly between eyes who received a total of 5 ranibizumab injections or more and those who did not receive 5 injections (p = 0.32, Fisher's exact test). As to the number of supplementary treatments in these two groups, the mean number was 0.5 ± 0.8 in eyes with total 5 injections or more and 0.3 ± 0.6 in those with less than 5 injections (p = 0.43, Mann–Whitney U test) (Table S3). Overall, the supplementary treatment led to a mean visual gain of 4.2 ± 11.4 letters, compared with 5.2 ± 10.0 letters in eyes without supplementary treatment at 12 months. Previously treated eyes and those with supplementary treatment after the loading phase seemed to have more sustained and smooth curves of central macular thickness (Fig. 5b, d). Two monthly ranibizumab reinjections were less likely to cause loss of vision at 12 months after the loading phase (Table 5). PSTA, macular laser or 2 ranibizumab reinjections, not in a monthly manner, were not associated with the loss of vision.

Discussion

While monthly injections of ranibizumab can lead to the significant improvement and long-term

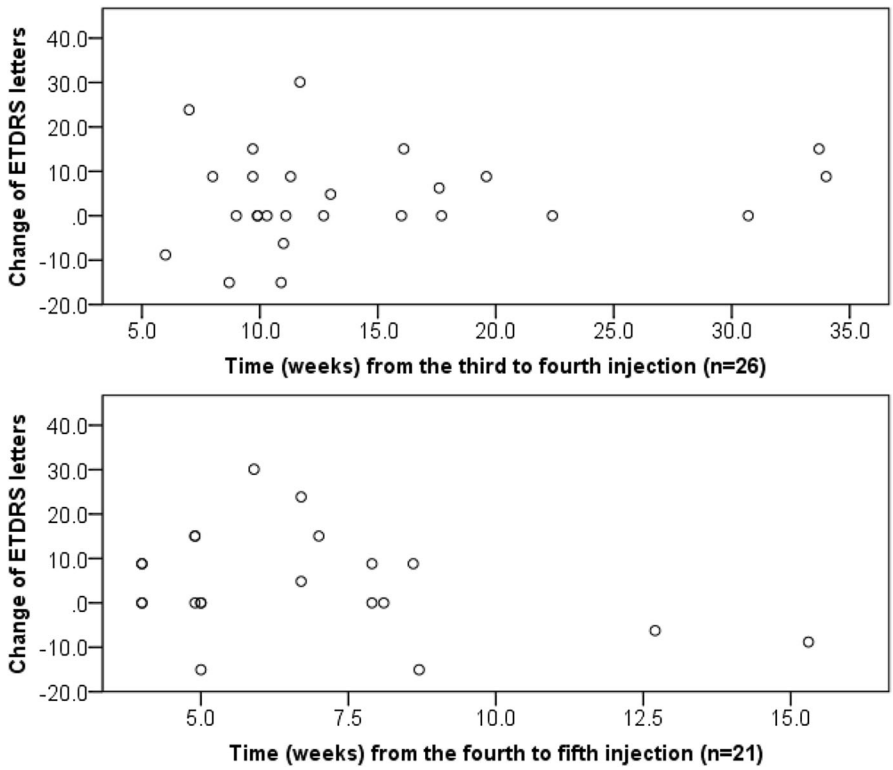

Fig. 4 Scatter plot shows the distribution of actual treatment time points between the 3rd and 4th injections (upper panel, total $n = 26$ eyes, shown as 25 with 1 overlapped circles), as well as the 4th and 5th injections (lower panel, total $n = 21$ eyes, shown as 17 with 4 overlapped circles) in relation to final visual change from the baseline. Shorter intervals between the 4th and 5th injections were associated with better visual outcome at 12 months ($r = -0.536$, $p = 0.027$, after adjusting for age, baseline vision, severity of diabetic retinopathy and the presence of previous treatment)

Table 2 Visual acuity status with or without completion of five injections

BCVA	6 months	9 months	12 months
Injection number < 5, $n = 18$			
Gain $\geq$ 10 letters	6 (33.3%)	7 (38.9%)	8 (44.4%)
Gain $\geq$ 15 letters	6 (33.3%)	6 (33.3%)	4 (22.2%)
Loss $\geq$ 10 letters	1 (5.6%)	1 (5.6%)	1 (5.6%)
Loss $\geq$ 15 letters	1 (5.6%)	1 (5.6%)	1 (5.6%)
Injection number ≥ 5, $n = 21$			
Gain $\geq$ 10 letters	5 (23.8%)	7 (33.3%)	9 (42.9%)
Gain $\geq$ 15 letters	2 (9.5%)	2 (9.5%)	5 (23.8%)
Loss $\geq$ 10 letters	2 (9.5%)	2 (9.5%)	3 (14.3%)
Loss $\geq$ 15 letters	1 (4.8%)	2 (9.5%)	2 (9.5%)

stabilization of visual and anatomical outcomes as seen in the RISE and RIDE study [11], in reality, three loading injections followed by pro re nata (PRN) treatment were more acceptable for most clinical scenarios [9, 10, 12, 13, 15]. Based on previous Asian studies, a minimum of 7 injections for 1 year may be required to maintain the efficacy [8, 13]. Such studies did not use a fixed number of injections. In Taiwan, however, a total of 5 injections can be obtained from the National Health Insurance for the first year, making it more difficult for treatment to follow the protocols as suggested by large trials. Our data showed an average gain of 5 letters at the end of the first year. The improvement was statistically significant compared with baseline, but a drop in vision after loading phase was also observed. This may be attributable to the time gap between 3rd and 4th injections, which not only came from the administrative process for application, but also the fact that physicians often stopped injections until recurrence of macular edema is observed.

We found that the inclusion criteria by the National Health Insurance tended to recruit a group of patients with worse baseline vision at a mean of 46.5 letters, which was lower than that of other studies ranging from approximately 55 to 63 letters [9, 10, 12, 13]. Worse baseline visions are more likely to have greater visual gain after treatment compared with better vision at baseline, making it difficult to encompass huge improvements [16]. In our study, there was a 40% gain of 10 letters or more, while previous reports yielded

Table 3 Final outcomes according to the number and status of retreatment of ranibizumab

Group	Baseline vision	Letters gain	Baseline CMT	CMT change
A (n = 18)	47.0 ± 18.1	5.4 ± 9.0	401 ± 114	− 80 ± 131
B (n = 21)	46.0 ± 12.9	4.5 ± 11.5	411 ± 99	− 75 ± 115
C (n = 15)	42.8 ± 13.6	7.1 ± 11.4	425 ± 109	− 81 ± 116
C1 (n = 7)	41.5 ± 11.8	9.0 ± 15.5	453 ± 116	− 87 ± 105
C2 (n = 8)	43.9 ± 15.6	5.5 ± 6.7	402 ± 105	− 77 ± 132

A. Total 5 injections not completed

B. Total 5 injections completed with or without monthly retreatment

C. Total 5 injections completed with monthly retreatment

C1. Monthly retreatment initiated before 6 months

C2. Monthly retreatment initiated after 6 months

Table 4 Baseline factors for change of ETDRS letters after loading treatment by multiple regression models

Category	B coefficient	p value
Age	− 0.23	0.177
Baseline BCVA	− 0.229	0.016
NPDR (reference) versus PDR	− 2.048	0.418
Previous treatment modality		
PSTA	− 4.186	0.36
Macular laser	− 7.872	0.079
Previous anti-VEGF agents	7.32	0.06

NPDR non-proliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy

varying results ranging from 24.8 to 43.1% of 10 letter gains at 1 year [8, 12, 13, 15]. Despite the ceiling effect, worse vision at baseline may also indicate an underlying severity and poor retinal function. Proliferative diabetic retinopathy, as seen in more than half of the present study, possibly limits the potential for visual recovery. Compared with moderate or severe non-proliferative retinopathy, proliferative diabetic retinopathy has a more negative impact on visual outcomes after ranibizumab treatment for macular edema [16, 17]. Caution needs to be taken to compare real-life outcomes with large trials that are based on stricter protocols.

It is worth mentioning that only six eyes with three mere loading injections in a year experienced a resolution of macular edema at 3 months, with CMT below 300 μm, while the other seven eyes had persistent edema. Under-treatment was apparent in these cases; however, we observed that even in cases where five total injections were completed, the visual outcome was not necessarily superior if patients were not retreated in a monthly manner. Another explanation could be the inadequate number of additional reinjections to produce an appreciable effect given the tight restriction on the total injection number. Subgroup analysis showed that eyes having consecutive monthly reinjections after their second application had gained more letters, with an average of 7.1 letters during the first year, particularly when the injections were initiated before 6 months (9.0 letters). This suggests that earlier and consecutive monthly retreatments may have a role in maintaining the efficacy achieved by the initial loading phase. While the number of patients in our study is small, this observation is meaningful particularly in the real-life setting wherein multiple injections are often not readily available.

Macular edema tended to recur after 6 months. Eyes with thicker baseline thickness could respond quite favorably to loading injections; however, they were also observed to rebound at higher frequencies when the coverage by these anti-VEGF agents became inadequate. In contrast, supplement PSTA or macular laser after loading treatment seemed to stabilize the macular thickness; however, this did not guarantee a corresponding improvement in vision. In the present study, we were more likely to treat patients with worse initial vision with these supplemental procedures. These eyes were usually more severe if not covered with adequate intravitreal injections and refractory to single treatment modality. Moreover, macular laser on

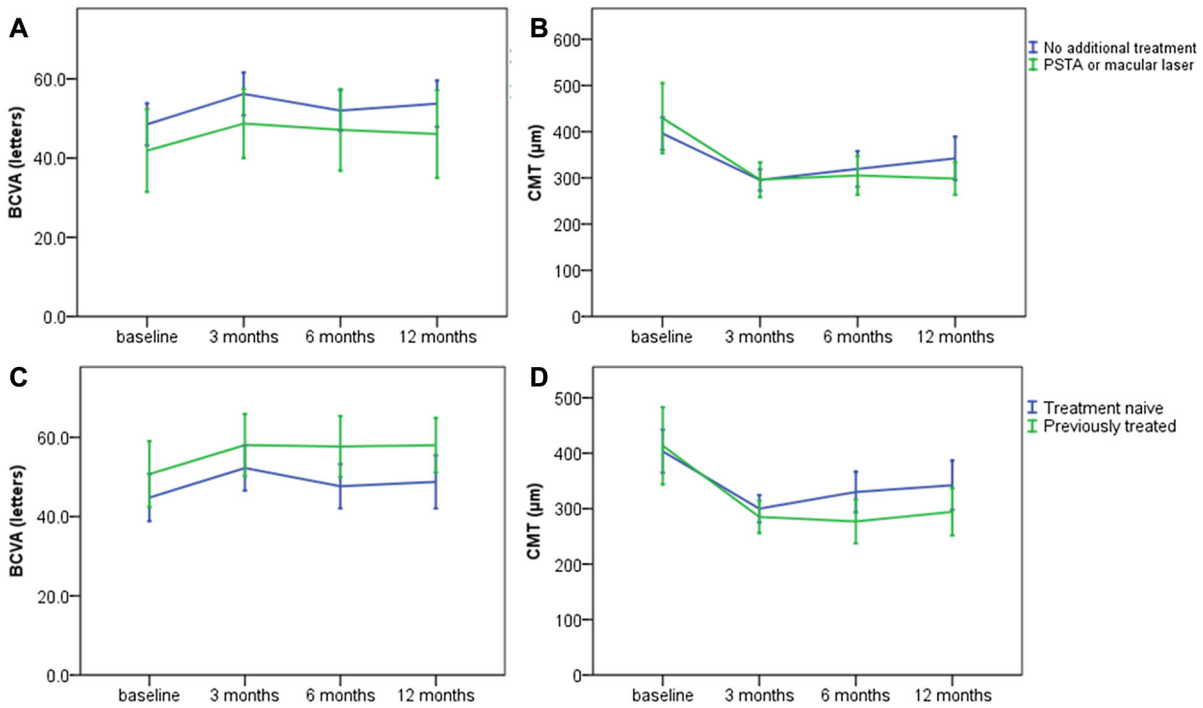

Fig. 5 Visual and anatomical outcomes in eyes having received additional treatments including PSTA or macular laser (n = 12) over the course of follow-up (**a**, **b**) and in eyes previously treated (n = 11) or treatment naïve (n = 28) (**c**, **d**)

Table 5 Correlation of retreatment factors to visual loss at 12 months after loading phase

Treatment modality	Visual loss > 10 letters		Visual loss > 15 letters	
	Coefficient	p value*	Coefficient	p value*
PSTA	− 0.059	0.737	0.016	0.928
Macular laser	0.217	0.211	0.026	0.883
Completion of five ranibizumab	− 0.084	0.632	− 0.029	0.870
Monthly reinjections	− 0.396	0.019	− 0.407	0.015

PSTA: posterior subtenon triamcinolone acetonide

p value* adjusted for baseline factors including age, baseline BCVA, severity of diabetic retinopathy, the presence of previous treatment

these eyes may not be beneficial or even have detrimental effects, which were observed in previous studies that early laser treatment is not better than deferring laser treatment when combined with intravitreal ranibizumab for DME [18, 19].

Our study provided further analysis on the effects of previous treatments. In the current study, the mean visual gain in previously treated eyes was 7.3 letters, while the value was 3.9 letters in treatment naïve eyes. The mean change in macular thickness in previously treated eyes was − 119 µm, while it was − 61 µm in treatment naïve eyes at 1 year. The data were not statistically significant, potentially because of the small sample size (p = 0.27 and 0.22, respectively, by Mann–Whitney U test). However, these suggested that prior treatments may still provide some benefit later in the course of follow-up, particularly for the maintenance of anatomical outcomes even if multiple injections were no longer obtained. An interesting observation was that previous treatment modalities,

though not statistically significant, might have different impacts on visual potentials following three loadings of ranibizumab (Table 4). Reduction of VEGF load by previous treatments may lower the efficacy of further anti-VEGF injections. While vision can be improved by previous treatments, further visual potential may be plagued in certain circumstances later on, such as cataract progression in steroid treatment or laser-related structural damage of RPE. In agreement with the conclusion from protocol I, triamcinolone with laser and deferred ranibizumab do not lead to the same visual potential as that of early ranibizumab [20]. The above may explain why previous PSTA and macular laser tended to have lower visual gain after the loading phase. However, mechanisms may differ in the explanation regarding previous anti-VEGF agents such as bevacizumab that had a positive impact on visual improvement. Recent literature has provided evidence of additional benefit from conversion between different anti-VEGF agents in the treatment of persistent macular edema [21–23]. Edema with partial or minimal response to previous bevacizumab may respond more favorably to ranibizumab. On a molecular basis, higher binding affinity of VEGF by ranibizumab or probable tachyphylaxis of bevacizumab may account for the observed results [24, 25].

Attempts have been made to investigate the drop in vision at 12 months after loading injections. Reinjections of two ranibizumab in a monthly manner, a concept similar to re-initiation of loading treatment, provide an important hint. Although fewer of such injections for the rest of the year may not obviously provide additional beneficial effects, we inferred that they might play a role in maintaining vision or minimizing visual loss. Previous studies failed to analyze associating factors for visual loss possibly due to the relatively small number of cases that existed for greater numbers of ranibizumab injections [17]. Other real-world report from PRIDE with a total of 617 patients, which employed three loading injections, had an average of 4–5 injections at 18 months [26]. The decline in visual gain after 6 months was observed after a year. Another study done by Brynskov et al. [27] showed a median increase of five letters at 1 year, followed by an average of five injections. In that particular study, 16% experienced a loss of vision that was five letters or more. All these studies employed a relatively lower number of injections and seemed to have greater proportions of visual loss.

There are certainly limitations in our study, such as its retrospective nature with a small sample size. We found that while 98 patients passed the first application, more than half (59 patients, 60.2%) were not included in our study due to multiple reasons, including incomplete loading treatment and loss of follow-up. Moreover, the timing of the last two reinjections as well as supplementary treatments was based on individualization that made difficult the protocol for standardization of retreatment. However, this limitation can also be seen as a strength of the study such that it gives an idea of how much potential this system could bring to patients under real-life settings, without necessarily following a strict protocol. Several studies have repeatedly suggested the importance of three or more loading injections to achieve the maximal effect. Varying clinical decisions were definitely affected by the limited number of reinjections available for reimbursement, reflecting the tough financial issue that the health insurance has been struggling with. Despite these limitations, we highlight some points, for example, that earlier and consecutive retreatment in a monthly manner may still be beneficial for patients.

In conclusion, an initial three consecutive injections of ranibizumab, followed by a maximum of three PRN reinjections with or without other supplementary treatments in 1 year, can effectively achieve clinical improvement for diabetic macular edema. Monthly reinjections for the completion of a total of 5 injections provided by the National Health Insurance within a year may lower chances of visual loss. We hope that this present study conveys helpful information to clinicians, especially when persistent multiple injections are not possible.

Compliance with ethical standards

Conflict of interest The authors declare that they have no any competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This research adhered to the tenets of the Declaration of Helsinki, and institutional review board (IRB) approval was obtained from the IRB

of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation.

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