• Clinical Research •

Prognostic factors of short-term outcomes of intravitreal ranibizumab in diabetic macular edema

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Abstract

• AIM: To evaluate the prognostic factors for short-term visual and anatomical improvement of intravitreal ranibizumab (IVR) for diabetic macular edema (DME).

• METHODS: Fifty-one eyes from 35 patients that received three consecutive monthly IVR for DME with moderate visual loss were retrospectively recruited; all cases had their baseline best-corrected visual acuity (BCVA) between 20/400 and 20/40. BCVA and central subfield thickness (CST) at baseline and month 3 were collected. Linear mixed models were used to evaluate the prognostic factors for visual and anatomical improvement at month 3.

• RESULTS: Younger age, poorer baseline BCVA and proliferative diabetic retinopathy (PDR) were correlated with better visual improvement at month 3 (*P*=0.002, 0.0001 and 0.007, respectively). Thicker CST and the presence of subretinal fluid at baseline were correlated with a greater reduction in CST (*P*<0.0001 and *P*=0.018, respectively). The presence of epiretinal membrane or previous posterior subtenon injection of triamcinolone acetonide (PSTA) were associated with a smaller reduction in CST (*P*=0.029 and 0.018, respectively), but had no significant effects in visual improvement at month 3 (*P*>0.05 for both).

• CONCLUSION: For eyes with DME and moderate visual loss, those with younger age, poorer baseline BCVA or PDR tend to have better visual improvement after three consecutive monthly IVR. Epiretinal membrane or previous PSTA result in less resolution of CST, but do not significantly affect visual improvement.

• KEYWORDS: diabetic macular edema; anti-vascular endothelial growth factor; ranibizumab; diabetic retinopathy; epiretinal membrane
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INTRODUCTION

The major causes of vision loss of diabetic retinopathy (DR) are diabetic macular edema (DME), tractional retinal detachment and neovascular glaucoma. Among these, DME is the most common cause of moderate vision loss[1-2]. DME is believed to result from hyperpermeability of the retinal vessels, in which vascular endothelial growth factors (VEGFs) play an important role[3]. It has been shown that monthly intravitreal injections of ranibizumab (IVR, Lucentis; Genentech, Inc., South San Francisco, CA, USA) resulted in visual acuity gain and anatomic improvement which sustained for three years[4-7].

Although most cases experienced significant visual gain and decreased central subfield thickness (CST) after ranibizumab treatment for DME, some cases had poor or no response[8]. Investigating the possible prognostic factors can help the clinicians make more informed decisions and provide the patients with more reasonable expectations for the treatment effects. Few studies have focused on the prognostic factors for visual improvement and anatomy recovery. The post-hoc studies from the Diabetic Retinopathy Clinical Research (DRCR.net) trial, the READ-2 trial and the RISE and RIDE trials have proposed the prognostic factors for the long-term visual outcomes after treatment for DME with ranibizumab[9-11]. However, prognostic factors for the short-term effects after IVR loading, which might be of equal concern for the patients, have not yet been investigated. In this study, we collected data from patients who had received three consecutive monthly IVR for DME and explored the prognostic factors for changes in visual acuity and CST at month 3.

SUBJECTS AND METHODS

Study Population This study retrospectively collected data from patients who had received three consecutive monthly IVR for DME at the Taipei Tzu Chi Hospital, Buddhist Tzu

Chi Medical Foundation between January 2013 and June 2014. The inclusion criteria included: 1) DR with focal or diffuse leakage in the macular area documented by fluorescein angiography (FA); 2) macular edema with a CST greater than 300 μm as documented by optical coherence tomography (OCT, Stratus; Carl Zeiss Meditec, Inc., Dublin, CA, USA); and 3) best-corrected visual acuity (BCVA) within 20/400 to 20/40 at baseline. The exclusion criteria included: 1) vitreomacular traction or tractional retinal detachment involving the macula; 2) serum HbA1c>10% at baseline; and 3) intravitreal injection of triamcinolone acetonide (IVTA), posterior subtenon injection of triamcinolone acetonide (PSTA), intravitreal injection of anti-VEGF other than ranibizumab, any retinal laser or any intraocular surgery from baseline to month 3 after IVR treatment.

The following data were collected for all cases: BCVA and OCT at month 0 (baseline), month 1 (1mo after 1st IVR), month 2 (1mo after 2nd IVR), and month 3 (1mo after 3rd IVR). BCVA was measured with Snellen charts and was converted to the logarithm of the minimum angle of resolution (logMAR). The severity of DR was classified first according to the appearance of panretinal photocoagulation (PRP) scar. Those with full PRP were categorized as the group of "Prior PRP". For those without visible PRP scar, the extent of DR was classified by FA as mild non-proliferative diabetic retinopathy (NPDR), moderate to severe NPDR, or proliferative diabetic retinopathy (PDR) according to the criteria proposed by the Global Diabetic Retinopathy Project Group. The following characteristics in OCT were recorded if they appeared in the central 1.5 mm-diameter area of fovea in either the horizontal or vertical cut of the macula: epiretinal membrane, subretinal fluid, hard exudate and cystic change. Macular grid laser or PSTA within 3mo before the 1st IVR were recorded, and no one had received IVTA or other anti-VEGF agents within 3mo according to the chart review. The following data at baseline were also recorded: body mass index (BMI), systolic blood pressure (SBP), insulin use, and lens status. These data were all candidates of the prognostic factors in the regression analysis for the treatment effect of ranibizumab for DME.

After the recruitment, a total of 51 eyes from 35 patients were enrolled in this study. This research adhered to the tenets of the Declaration of Helsinki, and approval was obtained from the Institutional Review Board of the Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation.

Statistical Analysis To capture the correlations between two eyes of the same patient, linear mixed models were used for comparison of logMAR of BCVA and CST between baseline and after treatment with the patient as a random effect. To evaluate the prognostic factors for changes in BCVA and CST at month 3, linear mixed models were used with the patient as a random effect. A *P* value less than 0.05 was considered statistically significant. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Table 1 Correlations between BCVA/CST and other baseline characteristics

Parameters at baseline	logMAR of BCVA		CST	
	Coefficient	*P*	Coefficient	*P*
Age (a)	0.0011	0.84	-2.56	0.043
Sex	0.046	0.72	-29.90	0.33
Severity of DR				
Mild NPDR (reference)	-	-	-	-
Moderate to severe NPDR	0.037	0.83	34.95	0.41
PDR	0.27	0.12	45.13	0.28
Prior PRP	-0.023	0.87	-13.83	0.69
OCT characteristics				
Epiretinal membrane	-0.19	0.12	-27.24	0.34
Subretinal fluid	0.096	0.52	-3.91	0.91
Hard exudate	0.049	0.71	-42.44	0.17
Cystic change	-0.085	0.52	0.44	0.99
Previous treatments				
Macular grid within 3mo	-0.12	0.42	-30.92	0.35
PSTA within 3mo	-0.051	0.74	-19.91	0.59
Lens status	-0.22	0.063	-1.10	0.97
Serum HbA1c (%)	-0.065	0.23	-21.05	0.096
BMI (kg/m^2)	-0.030	0.074	-9.07	0.059
SBP (mm Hg)	0.00049	0.87	0.80	0.25
Insulin use	-0.051	0.75	-53.83	0.15

BCVA: Best-corrected visual acuity; BMI: Body mass index, CST: Central subfield thickness; DR: Diabetic retinopathy; NPDR: Non proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; PRP: Panretinal photocoagulation; OCT: Optical coherence tomography; PSTA: Posterior subtenon injection of triamcinolone acetonide; SBP: Systolic blood pressure.

RESULTS

The mean age of the 35 patients was 61.2±10.1y (34 to 81y); 9 were female and 26 were male. For the 51 studied eyes, the mean logMAR of BCVA was 0.81±0.40 and the mean CST was 401±98 μm at baseline. The baseline logMAR of BCVA and CST were correlated to each other (correlating coefficient ρ=0.44, *P*=0.0013, Pearson correlation test). As for the other baseline characteristics, most of them were not correlated with baseline logMAR of BCVA or CST, except that older patients tended to have thinner CST (*P*=0.043, linear mixed model) (Table 1).

After three consecutive monthly IVR, the mean logMAR of BCVA improved from 0.81±0.40 at baseline to 0.69±0.40, 0.70±0.42 and 0.62±0.38 at months 1, 2 and 3, respectively (*P*=0.03, 0.02 and 0.0001, respectively, paired *t*-tests). Regarding the mean CST, it decreased from 401±98 μm at

baseline to 299±72 μm, 285±81 μm and 276±88 μm at months 1, 2 and 3, respectively (P <0.0001 for all, paired t-tests) (Figure 1).

Prognostic Factors for Visual Improvement at Month 3 After Three Consecutive Monthly Intravitreal Injection of Ranibizumab Younger age (P=0.002) and poorer baseline BCVA (P=0.0001) were correlated with more improvement in BCVA after the loading IVR treatment after adjustment for age, sex and baseline BCVA in linear mixed models. Compared with patients with mild NPDR, those with PDR tended to have more improvement in BCVA (0.33 more reduction in logMAR, P=0.007), while those with moderate to severe NPDR (P=0.69) or those with prior PRP (P=0.68) did not. None of the baseline characteristics in OCT, previous macular grid or PSTA, lens status, HbA1c, BMI, SBP or insulin use was correlated with BCVA improvement after IVR treatment (P>0.05 for all) (Table 2).

Prognostic Factors for Anatomical Improvement at Month 3 After Three Consecutive Monthly Intravitreal Injection of Ranibizumab Thicker baseline CST was correlated with a greater reduction in CST after the loading IVR treatments (P<0.0001) after adjustment for age, sex and baseline CST in linear mixed models. Compared to patients with mild NPDR, those with moderate to severe NPDR and those with PDR tended to have more of a reduction in CST in simple regression (109.85 μm, P=0.046 and 116.74 μm, P=0.034, respectively), but the differences were only of borderline significance in multiple regression (P=0.056 and P=0.076, respectively). Patients with epiretinal membrane at baseline tended to have a lower reduction in CST (50.07 μm less, P=0.047), while those with subretinal fluid at baseline tended to have a greater reduction in CST (72.42 μm more, P=0.018). Those who had received PSTA within 3mo before starting IVR tended to have a smaller reduction in CST (76.69 μm less, P=0.031). None of hard exudate or cystic change in OCT, previous macular grid, lens status, HbA1c, BMI, SBP or insulin use was correlated with CST change after IVR treatment after adjustment for age, sex and baseline CST (P>0.05 for all) (Table 3).

Correlations Between Visual/Anatomical Improvement and Optical Coherence Tomography Characteristics at Month 3 At month 3, none of the cases had subretinal fluid. Therefore, OCT characteristics including epiretinal membrane, hard exudate and cystic change were analyzed. Eyes with epiretinal membrane or cystic change at month 3 had poorer anatomical improvement at month 3 (53 μm and 27 μm reduction in CST, respectively) than those without epiretinal membrane or cystic change at month 3 (161 μm and 156 μm reduction in CST, respectively) (P=0.045 and P=0.0001, respectively by linear mixed models), but no significant difference in visual improvement were noted. Those who had hard exudate involving fovea at month 3 had poorer visual improvement (0.02 increase in logMAR of BCVA) than those without hard exudate at month 3 (0.25 reduction in logMAR of BCVA) (P=0.008 by linear mixed model), but not difference in change of CST were noted (Table 4).

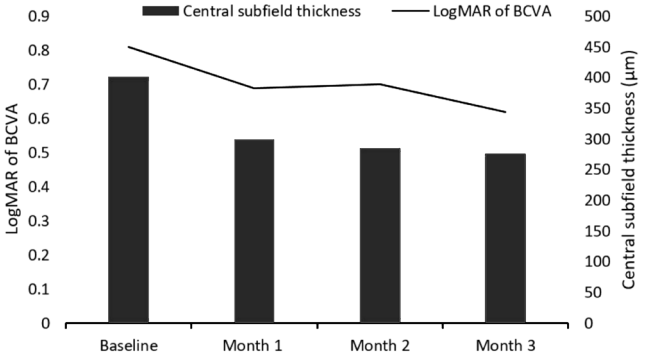

Figure 1 Changes in BCVA and central retinal thickness after three consecutive monthly IVR for DME.

Table 2 Prognostic factors for visual improvement at month 3 after three consecutive monthly intravitreal injections of ranibizumab

Parameters at baseline	Change of logMAR of BCVA at month 3			
	Simple regression		Adjusted for age, sex and baseline BCVA	
	Coefficient	P	Coefficient	P
Age (a)	0.016	0.009	0.012	0.002
Sex	-0.079	0.50	0.0072	0.94
LogMAR of BCVA	-0.40	0.0004	-0.42	0.0001
CST (μm)	-0.0016	0.0007	-0.00063	0.21
Severity of DR				
Mild NPDR (reference)	-	-	-	-
Moderate to severe NPDR	-0.078	0.54	0.049	0.69
PDR	-0.50	0.0002	-0.33	0.007
Prior PRP	0.038	0.72	0.037	0.68
OCT characteristics				
Epiretinal membrane	0.076	0.47	-0.057	0.54
Subretinal fluid	-0.092	0.47	-0.026	0.81
Hard exudate	0.17	0.12	0.073	0.45
Cystic change	0.16	0.15	0.12	0.19
Previous treatments				
Macular grid within 3mo	0.22	0.076	0.13	0.20
PSTA within 3mo	0.23	0.099	0.19	0.12
Lens status	0.10	0.31	0.022	0.80
Serum HbA1c (%)	0.075	0.10	0.024	0.57
BMI (kg/m^2)	0.032	0.023	0.021	0.085
SBP (mm Hg)	0.00099	0.70	0.0019	0.36
Insulin use	-0.0014	0.99	-0.032	0.78

BCVA: Best-corrected visual acuity; BMI: Body mass index, CST: Central subfield thickness; DR: Diabetic retinopathy; NPDR: Non proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; PRP: Panretinal photocoagulation; OCT: Optical coherence tomography; PSTA: Posterior subtenon injection of triamcinolone acetonide; SBP: Systolic blood pressure.

DISCUSSION

Ranibizumab has been proven to be a safe treatment for providing visual improvement, reduced risk of DR progression

Table 3 Prognostic factors for anatomical improvement at month 3 after three consecutive monthly intravitreal injections of ranibizumab

Parameters at baseline	Change of CST at month 3			
	Simple regression		Adjusted for age, sex and baseline CST	
	Coefficient	*P*	Coefficient	*P*
Age (a)	3.90	0.022	1.35	0.26
Sex	-10.17	0.81	-37.64	0.19
LogMAR of BCVA	-117.17	0.010	3.67	0.92
CST (μm)	-1.07	<0.0001	-1.07	<0.0001
Severity of DR				
Mild NPDR (reference)	-	-	-	-
Moderate to severe NPDR	-109.85	0.046	-73.09	0.056
PDR	-116.74	0.034	-65.68	0.076
Prior PRP	-3.93	0.93	-10.78	0.72
OCT characteristics				
Epiretinal membrane	87.72	0.025	50.07	0.047
Subretinal fluid	-75.28	0.12	-72.42	0.018
Hard exudate	62.45	0.14	8.11	0.78
Cystic change	36.53	0.39	33.91	0.22
Previous treatments				
Macular grid within 3mo	81.23	0.082	47.89	0.11
PSTA within 3mo	94.50	0.079	76.69	0.031
Lens status	-2.85	0.94	-3.33	0.90
Serum HbA1c (%)	34.40	0.050	4.91	0.71
BMI (kg/m^2)	14.27	0.008	5.11	0.18
SBP (mm Hg)	-1.20	0.22	-0.24	0.71
Insulin use	33.91	0.52	-26.16	0.45

BCVA: Best-corrected visual acuity; BMI: Body mass index, CST: Central subfield thickness; DR: Diabetic retinopathy; NPDR: Non proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; PRP: Panretinal photocoagulation; OCT: Optical coherence tomography; PSTA: Posterior subtenon injection of triamcinolone acetonide; SBP: Systolic blood pressure.

Table 4 Correlations between changes of BCVA/CST and characteristics in OCT at month 3

OCT characteristics at month 3	Change of logMAR of BCVA at month 3	*P*	Adjusted *P* value[a]	Change of CST at month 3	*P*	Adjusted *P* value[b]
Epiretinal membrane		0.27	0.70		0.005	0.045
Yes	-0.12±0.24			-53±75		
No	-0.24±0.38			-161±139		
Hard exudate		0.033	0.008		0.51	0.80
Yes	0.02±0.21			-99±101		
No	-0.25±0.35			-131±137		
Cystic change		0.19	0.48		0.002	0.0001
Yes	-0.08±0.26			-27±108		
No	-0.23±0.36			-156±123		

BCVA: Best-corrected visual acuity; CST: Central subfield thickness; logMAR: Logarithm of the minimum angle of resolution; OCT: Optical coherence tomography. [a]Adjusted for age, sex and baseline logMAR of BCVA by linear mixed model; [b]Adjusted for age, sex and baseline CST by linear mixed model.

and resolution of macular edema, with effects being detectable as early as 1wk after the initial IVR[12-15]. After three monthly loadings of IVR in the present study, the mean logMAR of BCVA decreased from 0.81 to 0.62 (*P*=0.0001), and the mean

CST decreased from 401 μm to 276 μm (P<0.0001) at month 3. These results are comparable with previous studies[12-15].

Despite the good results reported in the literature, there are patients who respond poorly to ranibizumab in daily clinical practice. It is important for patients to know what they can expect of the effects of the treatment based on their baseline status. Unfortunately, few studies have focused on the prognostic factors for visual improvement and anatomical outcomes after IVR for DME[9-11], and all of these evaluated the factors associated with only the long-term outcomes (at month 12 and 24, respectively). Clinically, many patients may be concerned about not only the long-term outcomes, but also the short-term ones. If there is no obvious visual or anatomical improvement after the loading treatment, the patients may feel frustrated and be less willing to receive further treatment. Therefore, the prognostic factors for changes in visual acuity and CST at month 3, which are clinically important, were explored in the present study.

According to the results of the present study, patients with younger age and poorer baseline BCVA tended to have better visual improvement after three monthly loadings of IVR for DME. These results are compatible with the long-term outcomes of "DRCR.net" and the RISE and RIDE studies, which showed that younger-aged patients and poorer baseline BCVA were associated with better long-term visual improvement[9-10]. This can be explained by the "ceiling effect", since those with a poorer baseline BCVA have more room for visual improvement. This ceiling effect can also explain why thicker baseline CST tends to have more of a reduction in CST in the present study as well as the "DRCR.net" study[9].

As for the effect of the severity of DR, we found that patients with PDR compared to those with mild NPDR were likely to have more improved vision after the loading of IVR for DME. However, those with prior PRP were not different from those with mild NPDR in visual improvement. According to the RISE and RIDE studies, those who received PRP prior to and during the trial tended to have poorer final BCVA, but experienced no difference in visual gain[10]. On the other hand, the report from the "DRCR.net" study showed that patients with severe NPDR had more visual improvement than those with mild to moderate NPDR and those with PDR or prior PRP[9]. This seems to contrast with our findings. When we categorized eyes with PDR into two groups, those with or without prior PRP, we found that improved vision was greater in those patients with PDR without PRP compared with PDR patients who had received PRP. In fact the improvement in visual acuity of eye with PDR treated with PRP were similar to those eyes with mild NPDR. As for the anatomical effect, patients with PDR or moderate to severe NPDR also tended to have a greater reduction in CST than those with mild NPDR, though the statistical significance was only borderline; and those with prior PRP showed no difference from those with mild NPDR in anatomical improvement. This could be explained by the presumed higher level of VEGF in the PDR group, insofar as anti-VEGF would theoretically produce the greatest effect in the PDR group even after the baseline BCVA was adjusted. For those with prior PRP, the VEGF level in the vitreous should be much lower than that in PDR patients without PRP. Therefore, the result was reasonable that the treatment effects in patients with prior PRP were similar to the effects in those with mild NPDR.

In the present study, patients with epiretinal membrane involving fovea tended to have less of a reduction in CST (P=0.025). This is reasonable because the epiretinal membrane itself may result in retinal thickening, thereby limiting the extent of reduction in CST. However, patients with DME and concurrent epiretinal membrane still experienced visual improvement after ranibizumab treatment. It was also confirmed by the result in this study that the existence of epiretinal membrane at month 3 was correlated with a thicker CST, but not with vision. According to the results of the "DRCR.net" study, patients with DME who showed evidence of surface wrinkling retinopathy had both poorer visual and anatomic improvement than those who had no surface wrinkling retinopathy at 1y. This was likely because in the "DRCR.net" study, "surface wrinkling retinopathy" was judged by fundus photography, which may represent either epiretinal membrane, vitreomacular traction or tractional retinal detachment, and all of these may result in progressive visual loss in the long run if there is no surgical intervention. In this study, we excluded cases with vitreomacular traction or tractional retinal detachment, which would be refractile to anti-VEGF. Given that the short-term effect in visual improvement was not affected by epiretinal membrane suggests that patients with DME and concurrent epiretinal membrane can still benefit from ranibizumab treatment. If patients with epiretinal membrane develop progressive retinal thickening after ranibizumab treatment in the long run, they should still receive surgical intervention.

For patients with subretinal fluid at baseline, ranibizumab had significantly more benefits in anatomical improvement than those without subretinal fluid. Previous studies also showed patients with subretinal fluid demonstrated better visual improvement[9-10]. As to the presence of hard exudate at fovea at baseline, it was found to have no correlation with either visual or anatomical improvement at month 3 in the present study. The presence of hard exudates was found be associated with more favorable visual outcomes in the "DRCR.net" and RISE and RIDE studies[9,16]. On the other hand, hard exudate was found to be a significant risk factor for poor visual outcome after macular grid laser treatment in the ETDRS study[17]. These contradictory results might be due to the

different treatment effects between ranibizumab and grid laser. Domalpally *et al*[16] has demonstrated that the resolution of hard exudate is not evident before 6mo of treatment. It means that visual impedance by hard exudate involving the fovea may persist until month 6 or later after ranibizumab treatment, and this could explain why in the present study better visual improvement was not noted at month 3 in those with hard exudate at baseline. To sum up the findings from the present and previous studies, for patients with DME and hard exudate involving fovea, longer recovery time with potentials of further visual improvement after month 3 can be expected after ranibizumab treatment.

PSTA has also been shown to effectively improve vision in patients with DME[18-21]. In the present study, patients who had received PSTA within 3mo before the ranibizumab treatment were found to have a smaller reduction in CST at month 3. It is possible that the previous PSTA had resulted in a partial reduction of CST in these patients, which means less of a residual potential for anatomical improvement. However, no difference in visual improvement was noted between those who had received PSTA before IVR and those who had not. Therefore, for patients with persistent macular edema after PSTA, ranibizumab can still offer significant visual improvement.

None of the systemic factors, including SBP, BMI, serum HbA1c level or insulin use, was correlated with short-term visual or anatomical improvement after ranibizumab treatment. These findings are consistent with the long-term outcomes of the "DRCR.net" study[9].

In conclusion, for patients with DME and moderate visual loss, those with younger age, poorer baseline vision and PDR without prior PRP tended to have better visual improvement at month 3 after three consecutive monthly IVR; those with thicker CST and subretinal fluid at baseline tended to have a higher CST reduction at month 3 after ranibizumab treatment. For patients with epiretinal membrane at baseline or having received PSTA within 3mo before, poorer anatomical improvement at month 3 after ranibizumab treatment was noted but the visual improvement was not affected by epiretinal membrane or previous PSTA.

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