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CLINICAL STUDY

The incidence and risk factors for the development of vitreomacular interface abnormality in diabetic macular edema treated with intravitreal injection of anti-VEGF

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Abstract

Purpose **To report the incidence and associated factors for the development of vitreomacular interface abnormality (VMIA) in patients with diabetic macular edema (DME) who received intravitreal injection (IVI) of anti-VEGF (Bevacizumab and Ranibizumab) treatment.**

Methods **A retrospective observational study. Patients with DME followed at least 6 months were reviewed. Baseline best-corrected visual acuity (BCVA), central retinal thickness (CRT) and final BCVA, CRT in eyes with and without VMIA were compared. Multiple logistic regression was also used to investigate the risk factors of VMIA formation in patients with DME treated by anti-VEGF.**

Results **A total of 201 eyes in 142 patients met the inclusion criteria of the study. VMIA developed in 44 eyes (21.89%) of patients during a mean follow-up period of 40.84 months. The estimated mean incidence of VMIA formation was 6.43% per year. Poor baseline BCVA was found to be a risk factor for VMIA development ($P = 0.001$, odds ratio = 5.299, 95% confidence interval: 1.972 to 14.238). There was no difference between eyes with and without VMIA formation in improving BCVA ($P = 0.557$) and lowering the macular edema (eyes without VMIA formation: $-107.72 \pm 171.91\,\mu$m; eyes with VMIA formation: $-155.02 \pm 212.27\,\mu$m, $P = 0.133$).**

Conclusions **This study revealed the incidence of VMIA formation in IVI anti-VEGF treated DME eyes was 6.43%. Poor baseline BCVA was found to be a risk factor for VMIA formation. Both eyes with and without VMIA development had favorable response to anti-VEGF treatment.**

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Introduction

Diabetic macular edema (DME) is the most frequent cause of visual loss in patients with diabetic retinopathy.[1] In the past, macular laser photocoagulation has been the standard treatment for DME for many years.[2] Recently, intravitreal anti-VEGF injection such as bevacizumab, ranibizumab and aflibercept has been found to be an effective treatment for reducing macular edema and improving the visual acuity of patients with DME.[3] Many clinical studies have revealed a beneficial effect of intravitreal injection (IVI) of anti-VEGF in both reducing macular edema and improving visual acuity in DME.[4,5]

As intravitreal anti-VEGF therapy has become increasingly popular in recent clinical practice for treatment of DME, concern about possible increases in ocular complications has become an important issue. Vitreomacular interface abnormality (VMIA) such as epiretinal membrane (ERM) or vitreomacular traction (VMT) is one of the most common complications associated with ocular surgical procedures. It is well known that ocular surgeries such as cataract extraction,[6–11] surgery for retinal detachment,[12,13] laser photocoagulation[7,12] and

retinal cryopexy procedures[12,14] are all associated with an increased incidence of ERM formation. As diabetic retinopathy and DME usually run a chronic and recurrent course, repeated intravitreal injection is often necessary to maintain the edema-suppressing effect. It is possible that repeated intraocular surgical procedures may have detrimental effects with formation of VMIA after a prolonged period. Although suppressing the VEGF level in PDR is beneficial for the suppression of fibrovascular membrane formation, several studies have reported paradoxical worsening of traction membranes associated with fibrovascular membranes in some patients with PDR.[15–17] To the best of our knowledge, it has still not been fully elucidated whether intravitreal anti-VEGF injections for treatment of DME, either from the repeated IVI procedures or from the anti-VEGF *per se*, affect the incidence of VMIA formation after a prolonged period.

In this study, we retrospectively investigated the incidence of VMIA formation in a group of patients with clinically significant DME treated with intravitreal anti-VEGF for at least 6 months. The influence of VMIA formation on the treatment effect of IVI anti-VEGF for DME was also investigated. To better understand the conditions associated with the formation of VMIA in DME patients treated with IVI anti-VEGF, several systemic and ocular factors including age, gender, hypertension, hyperlipidemia, mean level of glycosylated hemoglobin (HbA1c), best-corrected visual acuity (BCVA), central retinal thickness (CRT), prior cataract surgery, macular laser treatment and pan-retinal photocoagulation (PRP) were further analyzed.

Materials and methods

Patients recruitment

We conducted a retrospective study of patients with DME who received intravitreal injection (IVI) of anti-VEGF treatment (including Bevacizumab and Ranibizumab) at Shin Kong Wu Ho-Su Memorial Hospital from January 2006 to December 2014. Institutional review board/ethics committee approval and informed consents from the patients for anti-VEGF injections were obtained. The clinical records of all consecutive patients with DME were reviewed. The diagnosis of DME was made by the presence of exudative changes and thickening in the macula on ophthalmoscopic examination and evidence of late macular leakage on the fluorescein angiography (FA). Increased CRT or cystic change was observed on optical coherence tomography (OCT, Stratus, Carl Zeiss Meditec, Dublin, CA, USA, or RTvue, Optovue Inc., Fremont, CA, USA for patients enrolled between December 2013 and 2014). (All cases were kept using the same OCT examination throughout the follow-up period for the comparison of CRT). Eyes with evidence of VMIA at the initial visit were recorded and excluded from the study. Eligible patients were enrolled into this study according to defined inclusion and exclusion criteria. Inclusion criteria for our study were: an initial diagnosis of DME without VMIA made by ophthalmoscopy, FA and OCT (with regular follow-up for at least 6 months after the first diagnosis of DME). Eyes were excluded if they had any of the following conditions: (1) VMIA or vitreous hemorrhage before IVI treatment, (2) vitrectomy prior to or within 6 months of follow up period, (3) intravitreal corticosteroid injection prior to or within 6 months of the follow-up period, (4) Vitreous hemorrhage which precluded a detailed macular examination within 6 months of the follow-up period, and (5) concomitant ocular diseases such as posterior uveitis, advanced age-related macular degeneration or retinal vascular occlusions. Macular focal or grid laser, pan-retinal photocoagulation and cataract operation at baseline and during the follow-up period were recorded as items for subsequent analysis.

Treatment protocol

All patients received at least one anti-VEGF injection according to a standard aseptic operating procedure, which has been described in a previous study.[18] After injection, patients were examined 1 week after injection and then monthly thereafter. BCVA, intraocular pressure, slit-lamp biomicroscopy, dilated fundus ophthalmoscopy and OCT were performed at each visit. FA was performed only for eyes with suspected progression of diabetic retinopathy or macular ischemia. The injection was repeated at the treating physician's discretion if the BCVA or CRT deteriorated again after the first injection.

Data collection

BCVA was recorded in Snellen units and converted to logarithm of minimal angle of resolution (Log MAR) units for statistical analysis. The values were expressed as mean ± standard deviation.

The definition of VMIA in our study was characterized as typical features of ERM or VMT on both ophthalmoscopy and OCT examinations. The ophthalmoscopic features of VMIA were detected as shining or wrinkling reflections on or above the surface of the macula. The OCT characteristics of VMIA were classified into ERM and VMT according to a recent definition by 'The International Vitreomacular Traction Study Group', which devided the vitreo-macular interface features into 3 categories, namely, (1) vitreomacular adhesion (focal or broad adhesion of vitreous to inner retina without abnormal retinal changes),

(2) vitreomacular traction (focal or broad adhesion of vitreous to inner retina with retinal abnormal changes), (3) Full-thickness macular hole (with/without traction; small, medium, large;[19] Figure 1).[20,21] The OCT configurations of ERM were defined as partially separated or globally adherent membranes above the macular area according to the classification reported by Wilkins and associates (Figure 1).[20] Partially separated ERM were detected as thin but distinctive, highly reflective bands just above the inner surface of the retina with some focal attached points. Globally adherent membranes may be detected when various combinations of the following configurations had been noted: a macular pseudohole, a difference in optical reflectivity between the membrane and retina, or a visible membrane tuft or edge. The OCT configuration of VMT were defined as having the following 3 characteristics: (1) evidence of perifoveal vitreomacular adhesion; (2) macular attachment of the vitreous cortex within a 3-mm radius of the fovea; and (3) association of attachment with distortion of the foveal surface, intraretinal structural changes, elevation of the fovea above the RPE, or a combination thereof, but no full-thickness interruption of all retinal layers. Eyes with the development of full-thickness macular hole were also recorded.

Eyes were diagnosed with VMIA when an OCT configuration of ERM or VMT were detected in at least two of the six diagonal scans in the OCT examination associated with the characteristic findings previously described in the ophthalmoscopic examination, fundus photographs, or FA. Systemic conditions such as a history of hypertension, hyperlipidemia, macular grid or focal laser, PRP, and the level of HbA1c were also recorded during follow-up.

Data analysis

Wilcoxon signed-rank test was used to compare the mean age, mean HbA1c during follow-up, baseline BCVA, final BCVA, changes of BCVA, baseline CRT, final CRT, changes of CRT and the follow-up duration between patients who developed VMIA (VMIA (+) group) and who did not (VMIA (-) group). Mann–Whitney *U*-test was used to compare the baseline BCVA and CRT with the final BCVA and CRT in each of the two groups. We also compared the gender and the proportion of gender, hypertension, hyperlipidemia, cataract surgery, macular laser, and PRP between the two groups by the Chi-square test. Stepwise multiple logistic regression was also used to investigate the associations of the binary dependent

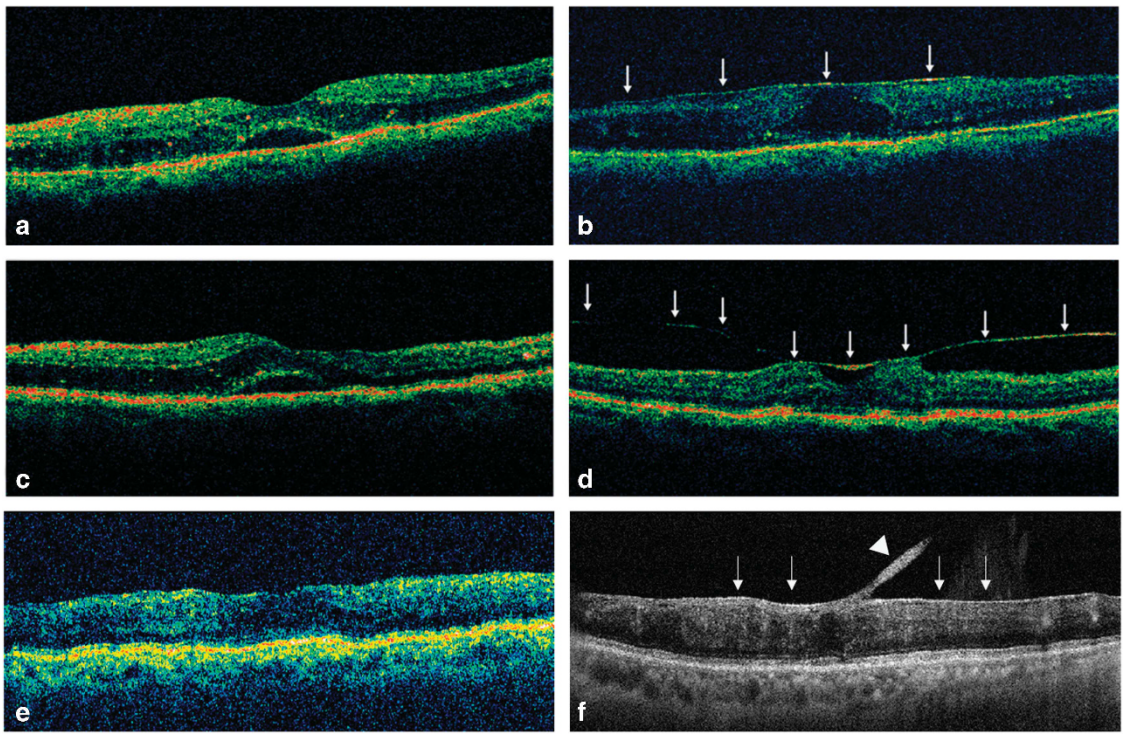

Figure 1 Representative optical coherence tomography (OCT) demonstrating the formation of vitreomacular interface abnormality (VMIA) in diabetic macular edema treated with intravitreal anti-VEGF (IVI). (a and b) OCT findings before (a) and after (b) development of epiretinal membrane (arrows). (c and d) OCT findings before (c) and after (d) development of VMT (arrows). (e and f) OCT findings before (e) and after (f, SD-OCT) development of ERM (arrows) with partially visible VMT (arrowhead).

variable 'presence of VMIA' with the continuous or categorical independent variables, such as age, hypertension, hyperlipidemia, mean HbA1c, cataract surgery, macular laser, PRP, baseline BCVA, and baseline CRT. SPSS 11.0 software (SPSS, Inc., Chicago, IL, USA) was used.

Results

Demographic data and overall treatment outcome

A total of 201 eyes in 142 patients who fulfilled the inclusion and exclusion criteria were included in this study (86 eyes in 70 patients found to have VMIA before IVI treatment had been excluded from the study) (Table 1). The mean age was 59.90 ± 9.29 years. There were 78 male and 64 female. The mean follow-up duration was 40.84 ± 24.88 months. A total of 865 IVI were performed, of which bevacizumab and ranibizumab were used in 721 (83.35%) and 144 injections (16.65%) of respectively. Each eye received a mean of 4.28 ± 3.67 injections during the follow-up period.

The mean baseline BCVA was 0.90 ± 0.51 Log MAR units (Snellen equivalent 6/48) and the mean final BCVA was 0.73 ± 0.50 Log MAR units (Snellen equivalent 6/32) (Table 1). The result showed that after a mean of 4.28 ± 3.67 injections, the final BCVA was significantly better than the baseline BCVA ($P = 0.027$), with improvement of BCVA by − 0.17 ± 0.43 Log MAR units.

The mean baseline CRT was 397.81 ± 153.55 μm and the final CRT was 278.92 ± 113.45 μm (Table 1). After IVI treatment, the final CRT were significantly lower than the baseline CRT ($P < 0.001$).

Incidence and factors associated with VMIA formation

Basic characteristics in eyes that developed VMIA and that did not develop VMIA were depicted in Table 2. Forty four eyes (21.89%) developed VMIA during the follow-up period. From these, 37 (18.52%) eyes in 26 patients were predominantly of the ERM configuration (2 eyes also had partial VMT) and 7 (3.37%) eyes in 7 patients had the VMT configuration on OCT (Figure 1). We did not find any case with development of full-thickness macular hole. The estimated mean incidence[22] of VMIA development (rate of VMIA formation/follow-up duration) was 6.43% per year (Table 1). The mean DME duration from the initiation of IVI to the VMIA detected was 16.27 ± 13.75 months.

Univariate analysis revealed that only a poor baseline BCVA was significantly associated with the development of VMIA in our study ($P < 0.001$). A thicker central subfield retinal thickness (CRT) was found to be associated with the development of VMIA with marginal significance ($P = 0.052$; Table 2). The correlation between initial BCVA and CRT was calculated to be 0.256, which revealed a low correlation between initial BCVA and

Table 1 Patients' clinical characteristics

Eyes (cases)	201 (142)
Male/female	78/64
Age (years)[a]	59.90 ±9.29
Hypertension	80 (56.34%)
Hyperlipidemia	72 (50.70%)
HbA1c (%)[a]	8.15 ± 1.56
Baseline BCVA (Log MAR)[a]	0.90 ± 0.51
Final BCVA (Log MAR)[a]	0.73 ± 0.50
Baseline CRT(μm)[a]	397.81 ± 153.55
Final CRT(μm)[a]	278.92 ± 113.45
Macular laser	77 (38.31%)
PRP	122 (60.70%)
Cataract surgery	86 (42.79%)
Follow-up (months)[a]	40.84 ± 24.88
Mean duration initial IVI to VMIA formation (months)[a]	16.27 ± 13.75
Mean injection times[a]	4.28 ± 3.67
Anti-VEGF	
Bevacizumab	83.35%
Ranibizumab	16.65%
Total incidence of VMIA	44 (21.89%)
Annual incidence of VMIA	6.43%

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; PRP, pan-retinal photocoagulation; VMIA, vitreomacular interface abnormality. [a]Data are presented as mean ± SD.

Table 2 Basic characteristics in VMIA (−) and VMIA (+) groups

	VMIA (−)	*VMIA (+)*	P-*value*
Eyes (cases)	157 (111)	44 (31)	
Male/Female	65/46	13/18	0.150
Age (years)[a]	59.87 ±9.26	60.02 ± 9.50	0.922
Hypertension (%)	99(81.82%)	19(79.17%)	0.760
Hyperlipidemia (%)[b]	74/95(77.89%)	18/21(85.71%)	0.423
HbA1c (%)[a]	8.09 ± 1.59	8.35 ± 1.42	0.371
Baseline BCVA (Log MAR)[a]	0.83 ± 0.48	1.17 ± 0.51	< 0.001*
Baseline CRT (μm)[a]	386.52 ± 157.78	439.60 ± 130.16	0.052
Macular laser (%)	57 (36.31%)	20 (45.45%)	0.353
PRP (%)	90 (57.32%)	32 (72.73%)	0.094
Cataract surgery (%)	66 (42.04%)	20 (45.45%)	0.816
Injection times[a]	4.06 ± 3.76	5.09 ± 3.26	0.099
Follow-up (months)[a]	40.22 ± 26.68	43.02 ± 27.52	0.511
Anti-VEGF (times)[a]			
Bevacizumab	3.45 ± 3.06	4.16 ± 3.05	0.156
Ranibizumab	0.61 ± 0.56	0.83 ± 0.75	0.203

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; PRP, pan-retinal photocoagulation; VMIA, vitreomacular interface abnormality; VMIA (+), eyes with VMIA formation; VMIA (−), eyes without VMIA formation.
Mann–Whitney *U*-test: age, HbA1c, BCVA, CRT. χ^2-test: gender, macular laser, PRP, and cataract surgery.
*$P < 0.05$. [a]Data are presented as mean ± SD. [b]Total number of patients with known lipid profile = 116.

CRT. Stepwise logistic regression also revealed that a poor baseline BCVA was the only risk factor associated with VMIA formation ($P=0.001$, odds ratio = 5.299, 95% confidence interval: 1.972 to 14.238). Other systemic or ocular factors such as age, hypertension, hyperlipidemia, HbA1c, anti-VEGF agents (percentage of bevacizumab or ranibizumab) number of injections, cataract operation, macular laser and PRP were all not significantly associated with VMIA formation (Table 3).

Table 3 Multivariate logistic regression analysis of VMIA formation

	OR (95% CI for OR)	P-*value*
Age	0.993 (0.941–1.047)	0.788
Hypertension	0.980 (0.412–2.333)	0.964
Hyperlipidemia	1.511 (0.636–3.590)	0.349
PRP	1.853 (0.679–5.055)	0.228
Macular laser	2.001 (0.820–4.881)	0.127
Cataract surgery	1.217 (0.489–3.030)	0.673
HbA1C	1.107 (0.832–1.472)	0.485
Injection times	1.037 (0.922–1.166)	0.545
Baseline BCVA	5.169 (1.920–13.917)	0.001*
Baseline CRT	1.001 (0.998–1.004)	0.485

Abbreviations: BCVA, best-corrected visual acuity; CI, confidence interval; CRT, central retinal thickness; OR, odds ratio; PRP, pan-retinal photocoagulation; VMIA, vitreomacular interface abnormality.
*$P<0.05$.

VMIA formation and final outcomes

The present study also revealed that VMIA formation seemed to reduce the effectiveness of anti-VEGF in the treatment of DME to a certain degree. Eyes without VMIA formation had significant improvement of BCVA from the baseline to final BCVA (0.83 ± 0.48 Log MAR units to 0.64 ± 0.45 Log MAR units, $P<0.001$), while in eyes with VMIA formation improvement of BCVA did not reach statistical significance (1.17 ± 0.51 Log MAR units to 1.03 ± 0.53 Log MAR units, $P=0.088$; Figure 2a). However, the changes from the baseline to the final BCVA were not significantly different ($P=0.557$) between eyes without VMIA formation (improved by -0.18 ± 0.39 Log MAR units) and eyes with VMIA formation (improved by -0.14 ± 0.54 Log MAR units). On the other hand, the formation of VMIA did not affect the improvement of macular edema in our study. The improvement from the baseline to final CRT was found to be statistically significant both in eyes without VMIA formation ($386.52\pm157.78\,\mu$m to $270.74\pm113.34\,\mu$m, $P<0.001$) and in eyes with VMIA formation ($439.60\pm130.16\,\mu$m to $311.67\pm109.25\,\mu$m, $P<0.001$) (Figure 2b). The changes from the baseline to the final CRT were not different in both groups (eyes without VMIA formation: $-107.72\pm171.91\,\mu$m; eyes with VMIA formation: $-155.02\pm212.27\,\mu$m, $P=0.133$).

Complications of IVI Anti-VEGF

No endophthalmitis, rhegmatogenous retinal detachment or vitreous hemorrhage was noted after any intravitreal injections. Also, no severe systemic adverse thromboembolic events such as cerebrovascular accidents, myocardial infarction or peripheral vascular disease were reported during follow-up.

Discussion

The current study investigated the incidence of the development of VMIA in DME patients with IVI Anti-VEGF treatment over a 40-month period, which, to the best of our knowledge, has rarely been reported in the literature. Our study revealed that 44 eyes (21.89%, 35 patients) of a total of 201 eyes who had been submitted to IVI treatment developed VMIA during a mean follow-up period of 40.84 months, which corresponds to an estimated mean incidence of 6.43%. Of 44 eyes that develop VMIA, 37 (18.52%) eyes were of the ERM configuration and 7 (3.37%) eyes had the features of VMT type (Figures 1c and d). The mean DME duration from the initiation of IVI to the VMIA detected was 16.27 ± 13.75 months.

We are not aware whether the estimated incidence of 6.43% per year of the new occurrence of VMIA in our patients with IVI treated DME is higher than that of the DME patients without IVI treatment, as we did not have a well-matched control for a reliable comparison. There were also very few large-scale reports about the incidence of VMIA formation in DME patients in the literature. We previously reported an incidence of 4.42% of new VMIA formation in a group of 76 DME patients (96 eyes) without IVI treatment.[18] The incidence of VMIA development of the IVI treated eyes in this study was seemingly higher than that of the non-IVI treated eyes in our previous study. However, considering that the basic characteristics were very different between patients in each group, it is still inconclusive whether or not IVI anti-VEGF would increase the incidence of VMIA formation.

Controversy exists regarding the effect of intravitreal anti-VEGF on the development or progression of fibrous membranes. As VEGF has been found to have an important role in the formation of VMIA in patients with diabetic retinopathy,[23,24] it is reasonable to postulate that IVI anti-VEGF may have an inhibitory effect on subsequent VMIA formation in most instances. However, anti-VEGF has been reported to lead to shrinkage and contracture of the fibrovascular membrane in diabetic retinopathy[15,17]and in retinopathy of prematurity;[25,26] this has raised concern of the possibility that IVI anti-VEGF

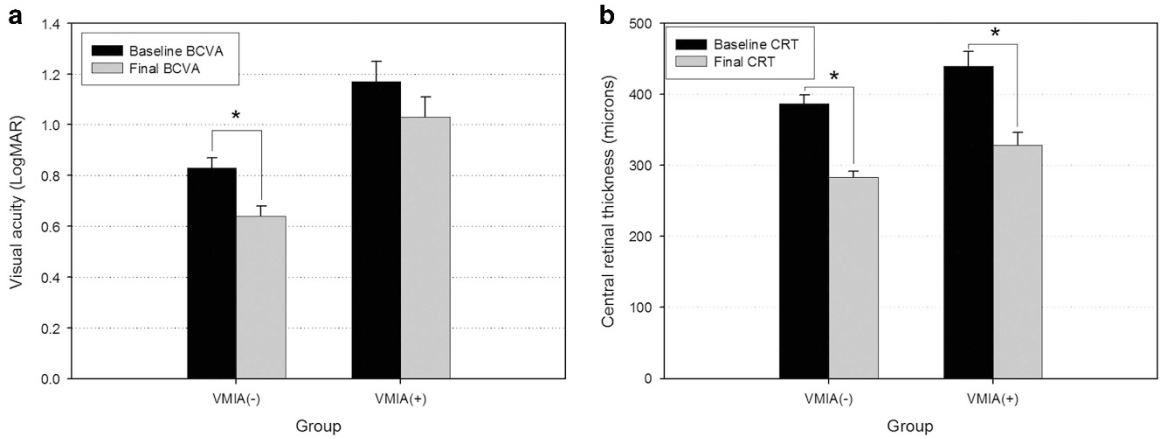

Figure 2 (a) The baseline BCVA and final BCVA in eyes with and without VMIA formation. (b) The baseline CRT and final CRT in eyes with and without VMIA formation. *$P<0.05$ by Wilcoxon signed-rank test. BCVA, best-corrected visual acuity; CRT, central retinal thickness; VMIA, Vitreomacular interface abnormality; VMIA (+), eyes with VMIA formation; VMIA (−), eyes without VMIA formation.

may paradoxically increase the incidence of VMIA formation in DME patients. Arevalo *et al*[16] had reported that this paradoxical progression of tractional retinal detachment occurred in only 11 out of 211 patients (5.2%) with PDR after IVI in a retrospective analysis. Considering the complex pathogenesis associated with the progression of the traction membrane in PDR, this percentage probably might not be sufficient to support that intravitreal anti-VEGF is a major factor for inducing the progression of tractional epiretinal membrane in eyes with diabetic retinopathy.

DME has been found to be associated with a high prevalence of VMIA (15.6–52.1%), and the prevalence seems to increase in proportion to the severity of DME.[21,27,28] Our studies investigated a group of eyes with clinically significant diabetic macular edema in which a substantial proportion (38.31%) did not respond well to the macular laser treatment. The studied eyes might be inherently prone to the development of VMIA. Thus, the occurrence of VMIA in 21.89% of eyes in our study after a mean of 40.84 months with IVI anti-VEGF treatment probably were not particularly high compared with the previous studies.

Our study also investigated the possible risk factors associated with the development of VMIA in DME patients with IVI anti-VEGF treatment. Older age has been identified as the most consistent risk factor associated with the formation of idiopathic ERM in many large population-based studies.[6,10,29–31] A previous study from our group also revealed that older age was associated with development of VMIA in a group of less severe DME without IVI treatment.[18] However, we observed no correlation between age and VMIA (most were of the ERM configuration) formation in DME patients with IVI treatment in this study. In the present study, initially poor BCVA was found to be the most important factor associated with the development of VMIA, either by using univariate analysis ($P<0.001$) or by stepwise logistic regression analysis ($P=0.001$, odds ratio = 5.299, 95% confidence interval: 1.972–14.238). Initial CRT was also found to be the second important factor associated with the VMIA formation during anti-VEGF treatment, however, the significance of this factor is only marginal ($P=0.052$). There was only a low correlation between the initial BCVA and CRT in our study. It is possible that as most eyes had severe or persistent clinically significant DME with high CRT, further increase in CRT may not exert further influence on the development of VMIA. Also the detection of VMIA may be more difficult in those patients with high CRT, which may result in underestimation of the contribution of CRT to the development of VMIA.

In the literature, cataract operation and thermal laser photocoagulation such as PRP has been well known to be associated with higher prevalence of VMIA formation.[6–12] However, in our study, these were not found to be associated with VMIA formation (Table 2). It is possible that our study size was too small to have enough statistical power to detect categorized risk factors for VMIA such as percentage of cataract operation or PRP for an infrequent complication like VMIA. Macular laser treatment, on the other hand, was less often found to be associated with VMIA formation.[27,28] The same result was also noted in our study (Table 2). Other systemic or ocular factors such as hypertension, hyperlipidemia, and level of HbA1c, were also found to have no significant correlation with the development of VMIA (Table 2). These factors were also less consistently found to be associated with the formation of VMIA in previous reports.[6,10,29–33]

The current study showed an improvement of BCVA and CRT at the final visit compared with baseline in eyes treated with IVI; the differences were statistically significant for both BCVA and CRT as expected. (BCVA: $P=0.027$, CRT: $P<0.001$). These results were not surprising as there have been many studies reporting that IVI is effective for both short-term and long-term treatment of DME. However, this study also revealed that anti-VEGF was less effective in improving the BCVA after the formation of VMIA. The improvement in BCVA was no longer significant in the group with VMIA formation ($P=0.088$) compared with the group without VMIA formation ($P<0.001$; Figure 2a), although the decrease in CRT in OCT findings were not significantly different between these two groups. Whether the existence of VMIA would influence the therapeutic effect of anti-VEGF on DME were not consistent in previous reports. Several studies reported that the effect of anti-VEGF was reduced in the treatment of DME with VMIA formation,[34,35] while Sadiq *et al*[36] in a recent prospective study (READ-3) reported that DME patients with vitreomacular adhesion without actual traction had a greater potential for improvement in visual outcomes with anti-VEGF therapy. Nevertheless, in our study, as the VMIAs were all newly formed during the treatment period, the tractional force was probably still very week and not enough to affect the macular thickness.

In summary, our study revealed that patients with clinically significant DME who underwent repeated IVI had a rate of VMIA formation in 21.89% of eyes during a follow-up period of 40.84 months, or an estimated incidence of 6.43% per year. Treatment with anti-VEGF probably would not significantly increase the incidence of VMIA formation compared with previous studies. This study also revealed that initial poor vision is associated with VMIA formation, which is further associated with reduced treatment effect of anti-VEGF. However, several limitations need to be noted. First, the retrospective, non-randomized design essentially precluded the enrollment of a well-matched control for head-to-head comparison. Second, our study started from 2006 when only time-domain OCT was available. The use of a time-domain OCT instead of spectra-domain OCT in most of our cases would probably be less sensitive to detect some fine or subtle VMIA formation. However, as the detection of VMIA in our study was conducted not only on OCT alone, but also by a constellation of repeated examinations including opthalmoscopy, fundus photography and FA, the sensitivity of detection of VMIA may be compensated to a large extent. Third, a mean injection number of 4.2 during a mean follow-up of 40.8 months in our 'real world' clinical practice settings (where most patients did not receive a reimbursement from insurance system in the study period) were obviously less than the optimal injection numbers. This less-than-optimal treatment condition seems to be a frequent phenomenon in other real-world settings even in groups where patients were covered by medical insurance.[37] Therefore, caution was advised when exploiting our results to other settings with more frequent and adequate IVI treatments for DME such as in randomized control trials. Nevertheless, the relative less responsiveness to IVI treatment in patients who developed VMIA revealed in this study may have clinical implications. Other treatment modalities such as vitrectomy with membrane peeling should be considered if VMIA formation severely impaired the visual and anatomic outcome. Further studies with prospective and case controlled designs are needed to verify these conclusions.

Summary

What was known before

- Vitreomacular interface abnormalities (VMIA) are a frequent complication in various macular disease including diabetic retinopathy and diabetic macular edema (DME).
- Various intraocular treatment may be associated with the formation of VMIA.
- There is very rare report about the incidence and risks for the development of VMIA during anti-VEGF treatment of diabetic macular edema despite this treatment has been a most common therapy in vitreoretinal practice.

What this study adds

- We find that: the annual incidence of VMIA formation is 6.43% in DME eyes treated with anti-VEGF.
- Poor baseline visual acuity is the most important risk factor for the development of VMIA during anti-VEGF treatment.
- Anti-VEGF is still effective in improving the BCVA and lowering the macular thickness in eyes where the VMIA developed, although the improvement in BCVA may be not as significant as eyes without VMIA development.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The approval to conduct the intravitreal injection of bevacizumab was obtained from the Institutional Review Board (IRB) of Shin Kong Wu Ho-Su Memorial Hospital (IRB no. 9709-001). The study adhered to the tenets of Declaration of Helsinki.

Author contributions

Design and conduct of the study (Cheng-Kuo Cheng); Collection, management, analysis, and interpretation of the data (Chun-Kai Chang, Cheng-Kuo Cheng, Chi-Hsien Peng); preparation, review and approval of the manuscript (Chun-Kai Chang and Cheng-Kuo Cheng).

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