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Combined intravitreal ranibizumab and posterior subtenon triamcinolone acetonide injections for patients with diabetic macular edema refractory to intravitreal ranibizumab monotherapy

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Abstract:

PURPOSE: The purpose of this study is to compare the efficacy of intravitreal ranibizumab (IVR) alone and concurrent IVR with posterior subtenon triamcinolone acetonide (PSTA) injection for patients with diabetic macular edema (DME) refractory to IVR monotherapy.

MATERIALS AND METHODS: We enrolled 43 eyes of 43 patients with DME who received at least three times of IVR, which resulted in poor anatomical responses, with central foveal thickness (CFT) reduction <10% and postinjection CFT >300 μm. All the eyes received initial 3 monthly then pro re nata (PRN) IVR 0.5-mg injections. Twenty eyes continued PRN injections and 23 eyes received combined IVR 0.5 mg and PSTA 40 mg with at least 1-year follow-up. Best-corrected visual acuity (BCVA) and CFT were recorded from 1-month to 1-year follow-up.

RESULTS: Following switch to combined therapy, the mean BCVA significantly improved from 0.61 ± 0.32 logarithm of the minimum angle of resolution (logMAR) to 0.45±0.39 logMAR at 6 month ($P = 0.003$), 0.43±0.35 logMAR at 9 months ($P < 0.001$), and 0.48±0.45 logMAR at 1 year ($P = 0.03$). In eyes with IVR alone, no significant VA improvement was noted throughout the year. Significantly better BCVA was noted in the combined group at 6-month, 9-month, and 1-year follow-up compared to IVR-alone group. The timing of combined therapy showed a significant association with 1-year BCVA ($t = 3.25$, $P = 0.018$).

CONCLUSION: Concurrent IVR and PSTA resulted in significantly better visual outcomes in 1-year follow-up for those refractory to preceding ranibizumab monotherapy for DME. Early addition of PSTA predicted a better visual outcome.

Keywords:

Intravitreal ranibizumab, posterior subtenon triamcinolone acetonide, refractory diabetic macular edema

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Introduction

Among diabetic patients, diabetic macular edema (DME) is the main cause of visual impairment.[1] Several large randomized controlled trials had proved the efficacy of intravitreal ranibizumab (IVR) against DME.[2,3] However, these studies also showed that not every patient responded well to such treatment. In the RESTORE study, 65% patients showed <5 letters of visual improvement at 1-year follow-up and 51% patients had central foveal thickness (CFT) >275 μm at 1-year follow-up.[2] Similar

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results were also found in DRCR.net Protocol I, which showed that 34.2% patients had visual improvement <5 letters and 40% patients had persistent DME at 3-year follow-up.[3]

According to previous studies, the production of neutralizing antibodies against antivascular endothelial growth factor (anti-VEGF) agents could cause tachyphylaxis of drug effects.[4] Another possible explanation is that there are not only anti-VEGF, but also several cytokines involved in the pathogenesis of DME, including monocyte chemoattractant protein 1, intercellular adhesion molecule 1 (ICAM-1), interleukin 6 (IL-6), and interleukin 8 (IL-8).[5-7] The anti-inflammation of corticosteroids could eliminate the effects of neutralizing antibodies and various cytokines involving in the formation of DME. Therefore, the addition of corticosteroids injection was reasonable to improve treatment response in cases with DME refractory to IVR. Furthermore, previous studies had shown that subtenon injection of triamcinolone acetonide was as effective as intravitreal injection of triamcinolone acetonide for DME.[8,9] Higher incidence of complications, such as elevated intraocular pressure (IOP), cataract formation, and endophthalmitis, was found following intravitreal injection of triamcinolone acetonide compared to subtenon administration.[8-10]

The purpose of this study is to evaluate the treatment responses and side effects of combined IVR and posterior subtenon injection of triamcinolone acetonide (PSTA) for patients with DME who responded poorly to IVR monotherapy. For comparison, we also collected and analyzed 1-year best-corrected visual acuity (BCVA) and CFT in eyes with IVR alone despite poor anatomical outcomes.

Methods

The protocol of the study which followed the Declaration of Helsinki was approved by the institutional review board of Far Eastern Memorial Hospital in Taiwan (approval number: 103152-F, approval date: January 2018). All the patients signed the informed consent to agree receiving intravitreal injections and participating in the study. This is a retrospective cohort study which included 43 eyes in 43 patients with center-involved DME who received IVR in Far Eastern Memorial Hospital from April 2015 to November 2016.

All participants in this study were of the same ethnicity (Taiwanese) with age more than 18 years and glycosylated hemoglobin (HbA1c) <10.0%. All patients had following baseline presentations: initial best corrected visual acuity (BCVA) ranging from 0.3 to 1.3 logMAR converted from Snellen chart measurement; central foveal thickness (CFT) more than 300μm in the 1-mm central macular area on spectral domain optical coherence tomography (SD-OCT, RTVue, Optovue Inc., San Francisco, CA, USA) using 6 radial line scans through the fovea; presence of macular leakage on fundus fluorescein angiography (FFA, TRC-NW7SF, Topcon Inc., Tokyo, Japan). The patients were allowed to be treated by panretinal photocoagulation, but vitrectomized eyes were excluded. Those who received ocular operation during the study period including cataract surgery or pars plana vitrectomy and those who developed vitreous hemorrhage, epiretinal membrane, or neovascular glaucoma were excluded from this study. Patients who received intravitreal injection of agents other than ranibizumab during the study period were also excluded. Pregnant or nursing women, patients with a history of thromboembolic events or major surgery within the previous 3 months, those with uncontrolled hypertension, those with prior macular photocoagulation or photodynamic therapy, and those with the presence of active infectious disease or intraocular inflammation were also excluded from the study.

All patients received 3 monthly injection of ranibizumab 0.5 mg and then received pro re nata (PRN) injection if CFT was >300 μm. In 23 eyes, PSTA 40 mg was added simultaneously with IVR if CFT reduction was <10% after preceding IVR. All patients completed at least 1 year of follow-up after combined therapy. Deferred macular laser was not added in any patient. Baseline data including age, gender, HbA1c, lens status, systemic hypertension, serum creatinine, and cholesterol level were collected. Patients' stage of diabetic retinopathy was determined by fundus color photography and FFA. The examinations of slit lamp, BCVA, IOP via pneumotonometer (CT-80, Topcon Inc., Tokyo, Japan), SD-OCT of macula, and dilated fundus examinations were performed at every monthly follow-up visit. We used the baseline SD-OCT scan as a reference during the follow-up scans. If IOP was >20 mmHg after injections during the follow-up visits, topical hypotensive agents were given. Visual testing was done in the same room at each visit. Their BCVA and CFT were recorded at 1-month, 3-month, 6-month, 9-month, and 1-year follow-up. The timing of combined therapy (treatment number of ranibizumab monotherapy before converting to combined treatment) was recorded. For comparison, we also collected patients' BCVA and CFT before and at 1-month after preceding IVR. Changes in CFT and BCVA were recorded and compared with Wilcoxon signed-rank test. The correlation of final BCVA with baseline data was analyzed with logistic regression. The CFT and BCVA of combined group and IVR alone group were compared with independent *t*-test. The adverse effects after combined therapy were analyzed. Statistical analyses were performed using SPSS for Windows (version 19.0, SPSS Inc., Chicago, IL, USA). The results were considered statistically significant if $P < 0.05$.

Results

Patients' basic characteristics are listed in Table 1. The mean age of the patients was 59.6 ± 8.1 years in the combined group and 63.3 ± 8.6 years in the IVR group. The mean HbA1c was 7.3% ± 1.0% and 7.9% ± 1.3% in the combined group and the IVR group, respectively. The mean serum creatinine level was 2.12 ± 2.87 mg/dL in the combined group and 1.98 ± 1.75 mg/dL in the IVR group. The mean total cholesterol in blood was 172.1 ± 49.9 mg/dL and 161.4 ± 34.6 mg/dL in the combined and the IVR groups, respectively. In the combined group, 12 patients (52.2%) showed proliferative diabetic retinopathy (PDR) and 11 (47.8%) of them had severe nonproliferative diabetic retinopathy (NPDR). Three (15%) patients showed moderate NPDR, 10 patients (50%) showed severe NPDR, and 7 patients (35%) had PDR in the IVR group. Sixteen patients (69.6%) and 12 patients (60%) were phakic in the combined and IVR groups, respectively. None of the above baseline characteristics including comorbidity of systemic hypertension, gender, BCVA, and CFT showed significant difference between the two groups.

In the combined IVR + PSTA group, average 3.5 ± 0.9 times (range 3–6 times) of ranibizumab monotherapy were given during a mean of 4.4 ± 1.7 months (range 2–7 months) before switching to combined therapy. The mean BCVA remained unchanged before (0.59 ± 0.39 logMAR) and after (0.59 ± 0.41 logMAR) purely ranibizumab treatment ($P = 0.924$). The mean CFT showed no significant reduction after IVR alone (before: 414.4 ± 78.6 μm; after: 428.17 ± 95.7 μm, $P = 0.291$). These refractory cases were given an addition of PSTA 40 mg to their regimen. The beginning of the combined therapy was defined as the baseline status. Baseline BCVA was 0.61 ± 0.32 logMAR on an average. These patients received an average of 5.7 ± 1.4 times of combined IVR and PSTA during 1-year follow-up. The mean BCVA at 1-month (0.58 ± 0.38 logMAR, $P = 0.58$) and 3-month (0.58 ± 0.40 logMAR, $P = 0.433$) follow-up did not significantly improved from baseline. However, BCVA at 6-month (0.45 ± 0.39 logMAR, $P = 0.003$), 9-month (0.43 ± 0.35 logMAR, $P < 0.001$), and 1-year (0.48 ± 0.45 logMAR, $P = 0.03$) follow-up showed significant improvement compared to those of baseline. Eleven eyes (47.8%) had visual improvement > 0.2 logMAR. Eight (34.8%) patients showed no visual gains at 1 year compared to that of baseline. Of these 8 patients, two of them were due to progressive cataract formation, three as persistent macular edema, two as recurrent macular edema, and one due to disruption of ellipsoid zone. Patients' age, gender, HbA1c, lens status, systemic hypertension, serum creatinine and cholesterol level, baseline BCVA, baseline CFT, and stage of diabetic retinopathy were not associated with 1-year BCVA ($P > 0.05$). The timing of combined therapy ($t = 3.25$, $P = 0.018$) showed significant association with 1-year BCVA.

On the other hand, BCVA remained unchanged from 1-month (0.50 ± 0.45 logMAR, $P = 0.058$), 3-month (0.51 ± 0.54 logMAR, $P = 0.132$), 6-month (0.61 ± 0.49 logMAR, $P = 0.697$), 9-month (0.59 ± 0.54 logMAR, $P = 0.972$), to 1-year (0.66 ± 0.50 logMAR, $P = 0.539$) follow-up compared to baseline (0.59 ± 0.44 logMAR) after an average of 5.9 ± 1.8 times of IVR monotherapy during 1-year follow-up. Significantly less patients (3/20, 15%) achieved BCVA improvement >0.2 logMAR at 1-year follow-up compared to combined group ($P = 0.022$). Twelve (60%) patients showed no visual gains at 1 year, all owing to persistent macular edema. Significantly better BCVA was noted in the combined group compared to IVR alone group at 6-month ($P = 0.043$), 9-month ($P = 0.042$), and 1-year ($P = 0.015$) follow-up.

In the combined group, the mean CFT showed significant reduction through 1-month (400.4 ± 84.0 μm, $P = 0.024$), 3-month (365.9 ± 68.3 μm, $P = 0.001$), 6-month

Table 1: Comparison of baseline data of combined intravitreal ranibizumab with posterior subtenon triamcinolone acetonide and intravitreal ranibizumab alone for diabetic macular edema

	Combined IVR + PSTA group (*n*=23)	IVR alone group (*n*=20)	*P*
Age (years)	59.6±8.1 (range: 43-79)	63.3±8.6 (range: 45-80)	0.154
Gender (male:female)	10:13	14:6	0.093
HbA1c (%)	7.3±1.0	7.9±1.3	0.127
Systemic hypertension (yes:no)	7:16	13:7	0.052
Serum creatinine (mg/dL)	2.12±2.87	1.98±1.75	0.855
Total cholesterol (mg/dL)	172.1±49.9	161.4±34.6	0.493
Lens status (phakic:pseudophakic)	16:7	12:8	0.064
DR stage (moderate NPDR:severe NPDR:PDR)	0:11:12	3:10:7	0.343
Central foveal thickness (μm)	468.1±128.2	470.2±120.5	0.956
Best-corrected visual acuity (logMAR)	0.61±0.32	0.59±0.44	0.847
Number of IVI before combined therapy	3.5±0.9 (range: 3-6)	N/A	
Duration of monotherapy before combined therapy (months)	4.4±1.7 (range: 2-7)	N/A	

HbA1c=Glycosylated hemoglobin, IVR=Intravitreal ranibizumab, PSTA=Posterior subtenon triamcinolone acetonide, NPDR=Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopathy, LogMAR=Logarithm of the minimum angle of resolution, IVI=Intravitreal injection

(365.0 ± 50.0 μm, $P < 0.001$), 9-month (368.0 ± 75.1 μm, $P = 0.002$), to 1-year (378.4 ± 84.2 μm, $P = 0.003$) follow-up compared to baseline (468.1 ± 128.2 μm). Ten eyes (43.5%) had CFT reduction >20%. Patients' age, gender, HbA1c, lens status, systemic hypertension, serum creatinine and cholesterol level, baseline BCVA or CFT, the timing of combined therapy, and stage of diabetic retinopathy were not associated with 1-year CFT ($P > 0.05$).

On the contrary, the mean CFT showed significant reduction at 1-month (340.6 ± 70.5 μm, $P < 0.001$), 3-month (379.7 ± 139.6 μm, $P = 0.044$), and 1-year (368.5 ± 100.3 μm, $P = 0.012$) follow-up but not at 6-month (430.9 ± 125.3 μm, $P = 0.273$) and 9-month (396.2 ± 109.3 μm, $P = 0.092$) follow-up compared to baseline (470.2 ± 120.5 μm) in the IVR-alone group. At 1-year follow-up, 9/20 (45%) eyes showed CFT reduction >20% compared to baseline. Significantly thinner CFT was noted in the combined group compared to IVR-alone group at 6-month ($P = 0.026$) and 9-month ($P = 0.045$) follow-up. The injection number was comparable between the two groups ($P = 0.822$). The BCVA and CFT change from baseline to 1-year follow-up of the two groups is demonstrated in Figures 1 and 2 and Table 2.

We performed a subgroup analysis on pseudophakic patients to eliminate the effect of progressive cataract formation [Figure 3]. Of the 7 pseudophakic patients in the combined group, persistent BCVA improvement was noted through 6-month (0.46 ± 0.56 logMAR, $P = 0.03$), 9-month (0.45 ± 0.56 logMAR, $P = 0.014$), to 1-year (0.47 ± 0.71 logMAR, $P = 0.042$) follow-up compared to baseline (0.69 ± 0.47 logMAR). However, BCVA remained unchanged throughout 1 year (1-month: 0.81 ± 0.65 logMAR, $P = 0.203$; 3-month: 0.85 ± 0.73 logMAR, $P = 0.934$; 6-month: 0.90 ± 0.65 logMAR, $P = 0.211$; 9-month: 0.98 ± 0.69 logMAR, $P = 0.548$; and 1-year follow-up: 0.79 ± 0.65 logMAR, $P = 0.876$) when compared to baseline (0.86 ± 0.64 logMAR) in the 8 pseudophakic eyes of IVR group.

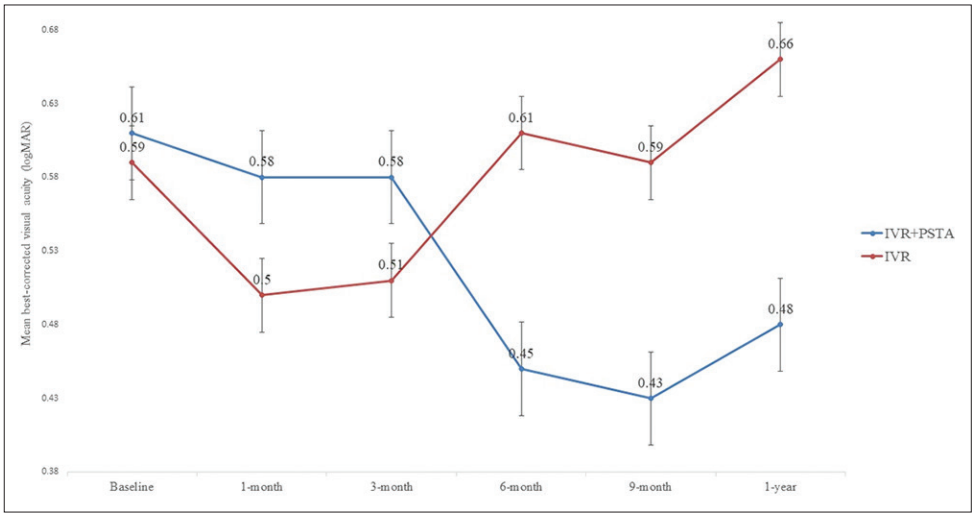

Figure 1: Best corrected visual acuity changes after continued intravitreal ranibizumab or combined intravitreal ranibizumab and posterior subtenon triamcinolone for all patients with diabetic macular edema during 1 year follow-up. IVR=Intravitreal ranibizumab, PSTA=Posterior subtenon triamcinolone acetonide, logMAR=Logarithm of the minimum angle of resolution

Table 2: Comparison of clinical data after treatment of combined intravitreal ranibizumab with posterior subtenon triamcinolone acetonide and intravitreal ranibizumab alone for diabetic macular edema

	Combined IVR + PSTA group (*n*=23)	IVR alone group (*n*=20)	*P*
1-month BCVA (logMAR)	0.58±0.38	0.50±0.45	0.123
3-month BCVA (logMAR)	0.58±0.40	0.51±0.54	0.125
6-month BCVA (logMAR)	0.45±0.39	0.61±0.49	0.043
9-month BCVA (logMAR)	0.43±0.35	0.59±0.54	0.042
1-year BCVA (logMAR)	0.48±0.45	0.66±0.50	0.015
1-month CFT (μm)	400.4±84.0	340.6±70.5	0.016
3-month CFT (μm)	365.9±68.3	379.7±139.6	0.244
6-month CFT (μm)	365.0±50.0	430.9±125.3	0.026
9-month CFT (μm)	368.0±75.1	396.2±109.3	0.045
1-year CFT (μm)	378.4±84.2	368.5±100.3	0.438
Rate of BCVA improvement >0.2 logMAR at 1 year, *n* (%)	11 (47.8)	3 (15)	0.022
Rate of CFT reduction >20% at 1 year, *n* (%)	10 (43.5)	9 (45)	0.466
Injection number	5.7±1.4 (range: 3-7)	5.9±1.8 (range: 3-10)	0.822

BCVA=Best-corrected visual acuity, CFT=Central foveal thickness, IVR=Intravitreal ranibizumab, PSTA=Posterior subtenon triamcinolone acetonide, LogMAR=Logarithm of the minimum angle of resolution

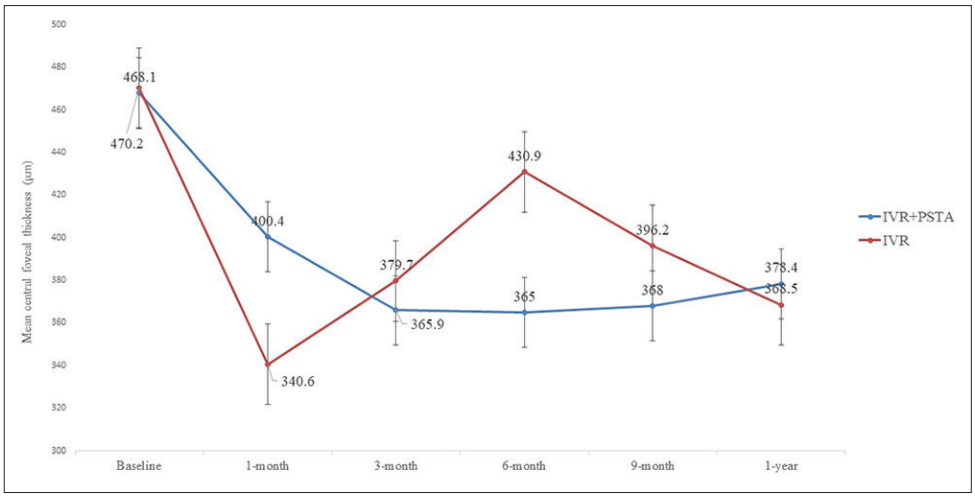

Figure 2: Central foveal thickness changes after continued intravitreal ranibizumab or combined intravitreal ranibizumab and posterior subtenon triamcinolone for patients with diabetic macular edema during 1 year follow-up. IVR=Intravitreal ranibizumab, PSTA=Posterior subtenon triamcinolone acetonide

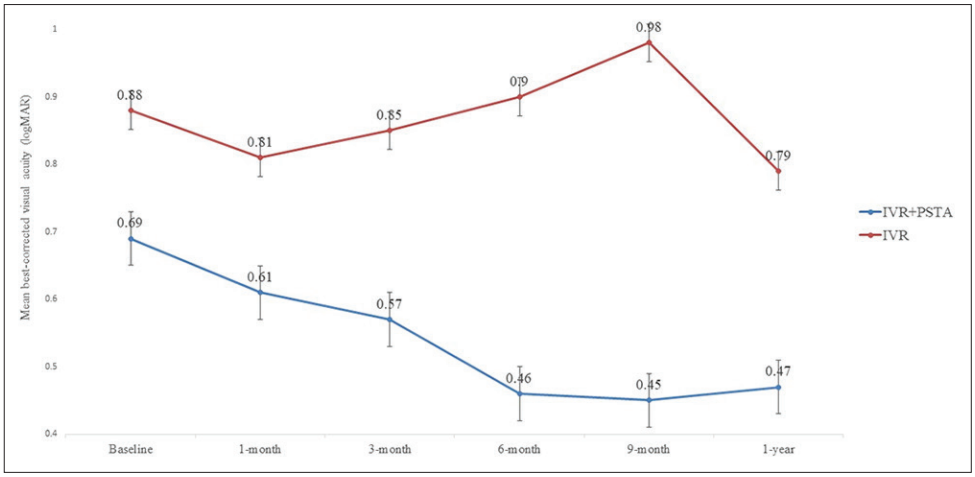

Figure 3: Best corrected visual acuity changes after continued intravitreal ranibizumab or combined intravitreal ranibizumab and posterior subtenon triamcinolone for pseudophakic patients with diabetic macular edema during 1 year follow-up. IVR=Intravitreal ranibizumab, PSTA=Posterior subtenon triamcinolone acetonide, logMAR=Logarithm of the minimum angle of resolution

We divided the morphology of DME into subretinal fluid (SRF), cystoid macular edema (CME), and SRF + CME. In these 43 eyes refractory to IVR treatment, 27 eyes had CME, 11 eyes had SRF, and 5 of them had SRF + CME. As for angiographic findings, we found that most of them had DR grading more than severe NPDR (21 eyes with severe NPDR, 19 eyes with PDR, and only 3 eyes with moderate NPDR).

There was no systemic thromboembolic event, retinal detachment, or infectious endophthalmitis following injections. In the combined group, aggravated cataract severity was found in 2 of 16 phakic eyes (12.5%). Only three patients (13.0%) developed ocular hypertension after combined therapy and required an average of 1.7 IOP-lowering agents. In IVR monotherapy group, no aggravated cataract formation or elevated IOP was found after treatments.

Discussion

Several large randomized controlled trials had found that a part of patients showed unfavorable treatment outcomes after IVR for DME. In DRCR.net Protocol I, CFT remained >250 μm at 3-year follow-up in 40% of patients.[3] This chronic persistent macular edema would cause damage to photoreceptors and result in poor and irreversible visual outcomes. In RESTORE study, 65% of patients showed <5 letters of visual improvement at 1-year follow-up. Even following 36 monthly injections of ranibizumab, still 40.9% of patients had final visual acuity worse than 20/40 in Snellen equivalent at the end of 3-year treatment course in RIDE study.[11] In our previous study which enrolled 60 patients with treatment-naïve DME, half of the patients had visual improvement <0.1 logMAR and 52% of the patients had CFT reduction <20% at 1-year follow up (unpublished data).

There is probably presence of neutralizing antibody to ranibizumab or elevated intraocular cytokines other than VEGF, which lead to edematous macula in patients with DME resistant to ranibizumab treatment.[4-7] There are several treatment strategies for ranibizumab-resistant DME. First of all, we can consider conversion of intravitreal injection to aflibercept, which has better inhibition against VEGF-B and placental growth factor compared to ranibizumab. In one study published by Rahimy *et al*., 50 diabetic eyes with persistent submacular fluid after 4 monthly injection of bevacizumab or ranibizumab showed significant visual improvement and macular thickness reduction after alteration to intravitreal aflibercept therapy.[12] In 57 eyes with DME recalcitrant to ranibizumab therapy, 59.6% of them were good responders after change to aflibercept treatment, but the rest of them (40.4%) responded poorly to aflibercept in our prior research.[13]

Corticosteroids are anti-inflammatory agents, in which intravitreal administration can reduce macular edema in diabetic eyes via inhibition of various intraocular cytokines including ICAM-1, IL-6, IL-8, and VEGF.[6] For eyes with DME poorly responding to ranibizumab, adding intravitreal corticosteroids on ranibizumab therapy or switching to intravitreal corticosteroids monotherapy can be another treatment choice. Iglicki *et al*. included 59 diabetic eyes refractory to intravitreal anti-VEGF agents and showed that changing to intravitreal dexamethasone implant treatment resulted in satisfactory clinical outcomes to reduce macular edema.[14] An obvious macular edema decrease was noticed after combined intravitreal dexamethasone implants and ranibizumab for cases with ranibizumab-resistant DME in DRCR.net Protocol U study.[15] Switching to intravitreal triamcinolone acetonide demonstrated significant visual and anatomical improvement in 64 eyes affected by DME refractory to anti-VEGF therapy.[16] Yolcu and Sobaci reported that combined intravitreal bevacizumab and triamcinolone resulted in nearly 0.2 logMAR visual gains and obvious macular edema reduction in 25 eyes with refractory DME to prior intravitreal bevacizumab or triamcinolone monotherapy.[17] However, the incidence of ocular hypertension which required treatments was as high as 32.97% after intravitreal dexamethasone implant injections for DME in a multicenter study.[18] Similar incidence of elevated IOP (38.3%) following intravitreal triamcinolone for DME was demonstrated in a previous research.[19] Intravitreal triamcinolone injection and PSTA demonstrated similar ability to ameliorate macular edema in patients with bilateral diffuse DME in a prior randomized study.[9] Intravitreal triamcinolone carried higher risks to induce IOP raising, cataract formation, and endophthalmitis than PSTA in a prior multicenter investigation.[8-10,20] Furthermore, PSTA showed 2.4 times lower risk of associated IOP elevation than anterior subtenon triamcinolone injection.[21] Therefore, we added PSTA on routine IVR for these refractory diabetic patients, in order to enhance the efficacy of macular edema control and lower the possibility of postinjection ocular hypertension.

Ercalik *et al*. compared the clinical effects of combined IVR and PSTA 40 mg and IVR monotherapy in 58 and 27 diabetic eyes with serous macular detachment for a 3-month period, respectively.[22] The visual improvement was comparable between the two groups both after the 1st and 3rd months. However, more serious macular detachment disappearance and higher postinjection IOP were found in 1 month after combined therapy. They found that the mean CFT dropped significantly from 543.9 μm to 334.0 μm at 1 month and 387.6 μm at 3-month follow-up in combined therapy group. In patients undergoing combined therapy, 23.8% and 18.6% of them showed more than 1-line improvement of BCVA at 1-month and 3-month follow-up. In our study, 13/23 (56.5%) achieved more than 1-line visual gains at 1-year follow-up. When compared to the study conducted by Ercalik *et al*., which included patients with only single IVR and PSTA injection and 3-month follow-up, our study provided data of PRN IVR and PSTA therapy and longer follow-up and confirmed sustained treatment effect of combined therapy. Eriş *et al*. included patients with DME having insufficient response to at least 6 anti-VEGF injections.[23] The authors compared subtenon triamcinolone plus anti-VEGF injections with anti-VEGF injections solely to manage patients with resistant DME for a 6-month period. Significant visual and anatomical improvement was only observed in the combined therapy group, but not in the anti-VEGF monotherapy group. This result was similar to our study. Our study showed that in patients with DME who did not have obvious response to preceding IVR monotherapy, significant visual gains and decreased macular thickness were found as soon as 1 month after simultaneous IVR and PSTA treatment. Significant visual improvement and macular thickness reduction maintained to 1 year following combined therapy. Furthermore, more than 40% of these ranibizumab-resistant patients showed satisfactory treatment response (BCVA gains >0.2 logMAR or CFT reduction >20%) after combined therapy for DME. Among those without visual increase at 1-year follow-up, only five of them were caused by persistent or refractory DME. However, the mean BCVA remained unchanged in the IVR monotherapy group throughout the year, in which 12 patients (60%) showed no visual improvement, all owing to refractory macular edema. Our study provided longer follow-up compared to the study conducted by Eriş *et al*., in which only 6-month data were provided. Furthermore, we showed complication rate of IOP elevation and cataract formation.

Adverse events associated with procedures of intravitreal injections and use of anti-VEGF were not discovered, such as systemic thromboembolic event, retinal detachment, or infectious endophthalmitis. Cataract aggravation and elevated IOP have been two major complications following peribulbar corticosteroid use. The DRCR.net study showed that IOP elevated in 17% of patients, and cataract extraction or worsening on clinical lens assessment occurred in 38% of patients after PSTA 40 mg.[24] Comparable results were found in this study. Three out of 23 patients (13.0%) developed ocular hypertension and required topical hypotensive agent treatments during 1 year. Two out of 16 phakic eyes (12.5%) developed progressive cataract formation with decreased BCVA at the end of 1 year.

To our knowledge, this is the first study to demonstrate the 1-year outcome of the clinical effects and adverse events of concurrent ranibizumab injection and PSTA for DME specifically refractory to ranibizumab monotherapy. Patients who had poor visual and anatomical outcomes after IVR solely showed satisfactory treatment response after combined IVR and PSTA 40 mg. The retrospective cohort study were performed in a single institution with limited case number, which were the major restrictions in this study. Prospective, multicentered, and large-scale research is required to confirm the efficacy of combined PSTA and IVR for refractory DME in the future.

Conclusion

Concurrent IVR and PSTA resulted in significant anatomical and visual improvement in 1-year follow-up for those who had poor outcome after preceding ranibizumab monotherapy for DME. Nearly half of the patients showed satisfactory response to the combined therapy. Early addition of PSTA can be considered while eyes with DME develop resistance to ranibizumab monotherapy. A part of participants developed progressive cataract formation and ocular hypertension after combined therapy. Monitoring IOP and crystalline lens status after combined therapy should be addressed.

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Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

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