• Clinical Research •

Comparison of intravitreal anti-vascular endothelial growth factor agents and treatment results in Irvine-Gass syndrome

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Abstract

● **AIM:** To compare the efficacy of bevacizumab, ranibizumab, and aflibercept in pseudophakic cystoid macular edema (CME) patients with Irvine-Gass syndrome (IGS).

● **METHODS:** This study is designed as retrospective consecutive case series. Those who developed postoperative pseudophakic CME that refractory to topical treatment and were treated with anti-vascular endothelial growth factor (VEGF) agents included in the study. Optical coherence tomography (OCT) examination including central macular thickness (CMT), total macular volume (TMV), retinal nerve fiber layer (RNFL), ganglion cell layer (GCL) and choroidal thickness (ChT) measurements at the baseline, 1st, 3rd and 6th month controls were performed.

● **RESULTS:** Fifty-nine eyes of 59 patients with CME and other healthy eyes of the patients (Control group) were evaluated. There were 22 eyes of 22 patients in the bevacizumab group (group 1), 19 eyes of 19 patients in the ranibizumab group (group 2), and 18 eyes of 18 patients in the aflibercept group (group 3). There was no difference in terms of age, gender, axial length, IOP, and spherical equivalent values. The baseline subfoveal and mean ChT were higher in the IGS group. The difference between the baseline and sixth month values of subfoveal and mean ChT were compared in the CME groups, thinning was observed in all three groups. GCL was thinner in the patient group at the 6th month of treatment. The resolution time of CME was observed faster in group 1.

● **CONCLUSION:** All three anti-VEGF agents seem to be effective in CME but bevacizumab appears to be slightly more cost-effective than the other two alternatives.

● **KEYWORDS:** anti-VEGF agents; choroidal thickness; ganglion cell complex; Irvine-Gass syndrome; macular edema

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INTRODUCTION

Irvine-Gass syndrome (IGS) is the most common cause of unexpected visual loss by causing cystoid macular edema (CME) after cataract surgery[1]. Although pseudophakic CME is predominantly developed after uncomplicated surgery, there is an increased risk of posterior capsule rupture, vitreous loss, and the use of iris retractors during the operation[2-3]. With the widespread use of spectral-domain optical coherence tomography (SD-OCT), the incidence of CME in all cases was found to be around 3.1%-41%[4]. However, the diagnosis rate of clinical significant CME with fundus fluorescein angiography (FFA) is between 1%-6%[3]. The presence of an epiretinal membrane, vascular occlusion, a history of uveitis or diabetes, and the use of prostaglandin drops also increase the incidence of pseudophakic CME[1,5]. The pathogenesis of CME is still unclear and most investigators suspect from the inflammation due to disrupted blood-retinal barrier. Although CME spontaneously regresses in the majority of IGS patients, treatment management remains unclear[5].

Topical therapies (non-steroid anti-inflammatory/steroid drops), oral acetozolamide, intravitreal triamcinolone/dexamethasone implant/anti-vascular endothelial growth factor (VEGF) injections, subcutaneous interferon, and vitrectomy have been reported to be used with different success rates[5-8]. In previous studies, it has been reported that intravitreal anti-VEGF agents (pegaptanib sodium[6], bevacizumab[9], ranibizumab[8], aflibercept[10]) provide anatomical and visual improvement in patients with macular edema due to vascular leakage. The aim of this study was to compare the efficacy of bevacizumab, ranibizumab, and aflibercept in naive pseudophakic CME

patients and to compare the OCT results of these patients with fellow healthy eyes that underwent uncomplicated cataract surgery.

SUBJECTS AND METHODS

Ethical Approval This descriptive, observational, retrospective, consecutive, case series study was approved by the Local Ethics Committee, and was conducted according to the principles of the Helsinki Declaration. All subjects were informed about the study procedure, and written consent was obtained.

Among the patients who underwent phacoemulsification surgery with posterior chamber intraocular lens implantation between 2015 and 2019, those who developed postoperative pseudophakic CME that refractory to topical treatment (indomethacin 0.1%, 3 times daily for 3mo) and were treated with anti-VEGF agents were included in the study.

Measurements of the fellow eyes of patients with IGS 6mo after cataract surgery were included in the study as a control group. All individuals with <21 mm or >24 mm axial length, significant refractive errors (>3 diopters of spherical equivalent refraction), intraocular pressure (IOP) ≥21 mm Hg, retinal vascular diseases, uveitis, glaucoma, pseudoexfoliation, patients who had previous other ocular surgery, presence of any macular degeneration type/epiretinal membrane *etc*., and smokers or ex-smokers were excluded from the analysis. Patients who did not continue their follow-up after intravitreal injection were also excluded from the study. Comorbidities of patients, such as hypertension (HT) and diabetes mellitus (DM), were noted.

Before the intravitreal injections, topical 5% povidone-iodine was applied on the ocular surface and periorbital area washed using povidone-iodine. An intravitreal injection 1.25 mg/0.05 mL of bevacizumab, 0.5 mg/0.05 mL of ranibizumab, and 2.0 mg/0.05 mL of aflibercept was administered *via* inferotemporal approach through the pars plana by a 30-gauge needle. None of the cases included in the study were reported to have had an adverse reaction to the intravitreal anti-VEGF injected.

All patients underwent a complete ophthalmologic examination [best corrected visual acuity (BCVA), IOP, OCT (RS-3000, Nidek, Gamagori, Japan) examination including central macular thickness (CMT), total macular volume (TMV), and choroidal thickness (ChT)] at the baseline, 1st, 3rd, and 6th month controls (Figure 1). The control group and all participants in the 6th month of their follow-up [(BCVA, IOP, OCT examination including CMT, TMV, ChT, macula, retinal nerve fiber layer (RNFL), and ganglion cell layer (GCL)] measurements were performed. Macular thickness, RNFL and GCL values obtained from scanning were calculated automatically by the device. The macular thickness was

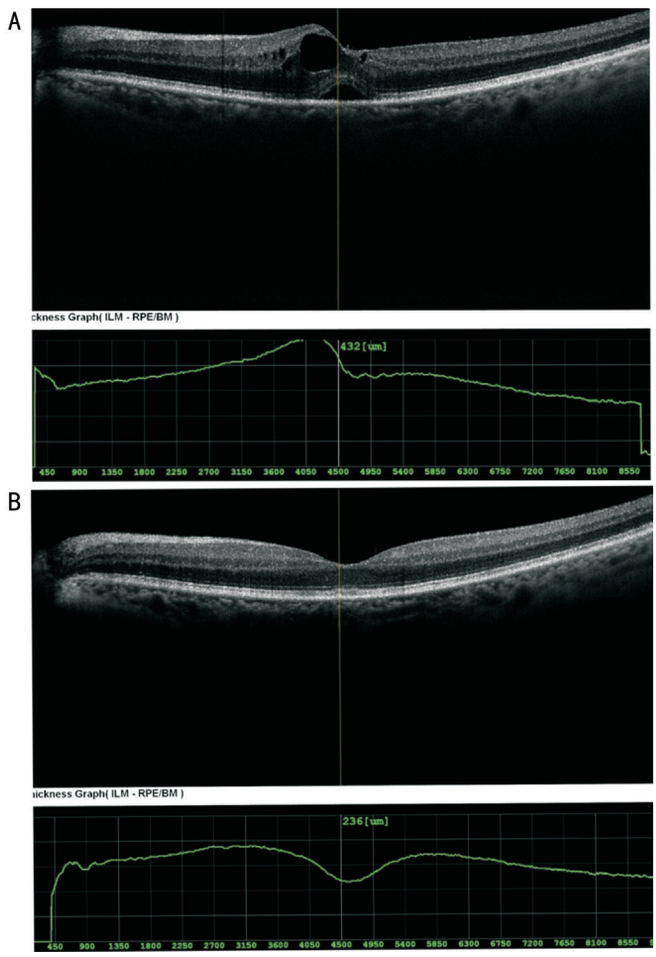

Figure 1 Image of macular OCT before (A) and 6mo after (B) bevacizumab injection.

evaluated by dividing to 9 ETDRS section (center, inner and outer temporal/superior/nasal/inferior). RNFL was evaluated by dividing into 5 quadrants (whole, temporal, superior, nasal, inferior). GCL was divided into 8 regions (inner and outer inferotemporal/inferonasal/superotemporal/superonasal) and the average of these 8 regions were evaluated. For ChT values, 3 lines at nasal and temporal were drawn at 1000 microns intervals, centering the subfoveal sclerochoroidal junction.

Statistical Analysis Analysis of the data was performed in the SPSS 23 for Windows (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) program. The descriptive statistics were expressed as mean±standard deviation for variables with normal distribution, median (quartile range) for non-normal distributions, and number of cases and (%) for nominal variables. Pearson Chi-square test and Fisher's Exact test were used for comparison of descriptive statistics, as well as qualitative data. The Kolmogorov-Smirnov distribution test was used to examine the normal distribution. Mann-Whitney *U* test was performed for comparison of non-normally distributed quantitative data of two groups; Student's *t*-test was used for normal distributed data. Kruskal-Wallis test was performed for comparison among more than two groups

Table 1 Demographic and structural characteristics of the groups and their comparisons mean±SD

Items	Controls (*n*=59)	Group 1 (*n*=22)	Group 2 (*n*=19)	Group 3 (*n*=18)	*P*
Age (y)	62.5±5.3	64.6±6.4	60.4±4.5	64.2±1.7	0.237
Gender (female/male)	25/34	9/13	8/11	8/10	0.469
Comorbidity (*n*)					0.999
HT		11	10	9	
DM		3	3	2	
HT+DM		3	2	3	
Axial length (mm)	23.1±0.5	23.3±0.5	23.4±0.5	23.4±0.4	0.290
Spherical equivalant (D)	0.28±0.66	0.37±0.81	0.39±0.87	1.25±0.93	0.104
Intraocular pressure (mm Hg)	16.2±1.8	15.3±3.1	15.1±2.1	17.5±3.9	0.417
Resolution time of CME (mo)	-	2.0±1.05	3.5±1.45	3.6±1.96	0.031
Initial BCVA (logMAR)	-	0.96±0.18	0.89±0.23	0.94±0.22	0.599
Final BCVA (logMAR)	-	0.23±0.19	0.19±0.18	0.21±0.08	0.666
Average No. of injections	-	1.8±0.7	2.0±0.6	1.8±0.7	0.925

D: Diopter; CME: Cystoid macular edema; BCVA: Best corrected visual acuity; HT: Hypertension; DM: Diabetes mellitus.

of non-normally distributed quantitative data, and Mann-Whitney *U* test was performed to analyze the group causing the difference. For comparison among more than two groups of normally distributed quantitative data, ANOVA test was performed and the group causing the difference is defined with post hoc Tukey test. Pearson test was used to investigate the relationship between normally distributed quantitative data; the Spearman test was used to examine the relationship between non-normally distributed quantitative data. The results were evaluated at 95% confidence interval, $P<0.05$ significance level.

RESULTS

Fifty-nine eyes of 59 patients with IGS and other healthy eyes of the patients (Control group) were evaluated. There were 22 eyes of 22 patients in the bevacizumab group (group 1), 19 eyes of 19 patients in the ranibizumab group (group 2), and 18 eyes of 18 patients in the aflibercept group (group 3). There was no difference among the groups in terms of age, gender, axial length, IOP, and spherical equivalent values. Also, there was no difference among the groups in terms of the distribution of comorbidities. The demographic and structural characteristics of the control and IGS groups and their comparisons are summarized in Table 1. There was no difference between BCVA at the end of 6th month in three agents (Figure 2). When CMT and TMV was evaluated among the IGS groups (groups 1-3), the groups were similar in the baseline and last follow up (Figure 3; Table 2). Also, there was no difference observed between all 9 ETDRS sections of the macula of the patient group in the 6th month and the control group (Table 3). When the comparison was made between the control group and the IGS groups, the baseline subfoveal and mean ChT were higher in the IGS group as shown in Table 2. However, ChT was similar at 3 and 6mo. On the basis of this,

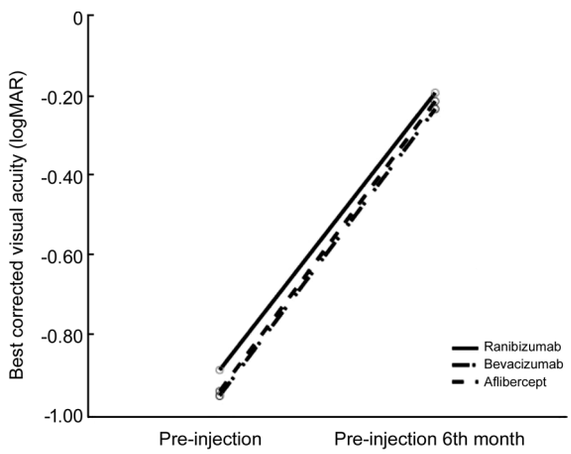

Figure 2 Time-lapse improvement in BCVA after injection of anti-VEGF agents.

when the difference between the baseline and 6th month values of subfoveal and mean ChT was compared in the IGS groups, thinning was observed in all three groups (Table 2).

When RNFL thicknesses between control and patient groups were evaluated, the thicknesses were similar in all quadrants (whole, temporal, superior, nasal, inferior; Table 4). When we compared GCL values between control and IGS groups, we observed that the inner GCL was thinner in the patient group at the 6th month of treatment. However, there was no significant difference among IGS groups (Table 4).

When comparison was made among the IGS groups, there was no significant difference at baseline and 6th month macular, RNFL, GCL, and ChT (Tables 3, 4). However, when the resolution time of CME was compared between the groups, it was observed that there was a faster resolution in group 1 (Table 1).

DISCUSSION

Although CME after cataract surgery usually regresses spontaneously, treatment is rarely needed[11]. Treatment of IGS

Table 2 Comparison of macular and choroidal thicknesses within and between groups mean (SD)

Regions	Controls (*n*=59)	Group 1 (*n*=22)	Group 2 (*n*=19)	Group 3 (*n*=18)	*P*
Baseline					
CMT (μm)	N/A	555.5 (238.5)	553.5 (125.5)	540.0 (64.5)	0.901
TMV (μm^3)	N/A	10.2 (1.6)	9.9 (1.1)	10.2 (1.9)	0.721
Subfoveal ChT (μm)	N/A	246.5 (29.7)	271.5 (52.7)	261.5 (47.7)	0.137
Nasal ChT (μm)	N/A	219.0 (40.5)	235.5 (44.0)	217.5 (43.2)	0.371
Temporal ChT (μm)	N/A	229.5 (22.0)	230.5 (23.2)	230.0 (55.5)	0.693
Mean ChT (μm)	N/A	232.0 (26.4)	248.0 (35.5)	239.6 (43.0)	0.313
6th month					
CMT (μm)	216.5 (20.3)	213.5 (21.1)[a]	226.6 (18.1)[a]	227.7 (39.5)[a]	0.168
TMV (μm^3)	7.5 (1.0)	7.6 (1.2)[a]	7.5 (1.1)[a]	7.5 (1.1)[a]	0.930
Subfoveal ChT (μm)	217.0 (56.5)	206.5 (42.7)[a]	235.0 (43.0)[a]	233.5 (59.0)[a]	0.345
Nasal ChT (μm)	201.1 (61.3)	198.5 (14.7)[a]	221.5 (46.0)[a]	208.0 (37.2)	0.796
Temporal ChT (μm)	214.7 (51.8)	200.0 (48.7)[a]	221.5 (47.5)[a]	198.0 (54.2)[a]	0.744
Mean ChT (μm)	210.1 (58.9)	206.8 (26.1)[a]	226.5 (47.5)[a]	215.0 (48.4)[a]	0.624

CMT: Central macular thickness; TMV: Total macular volume; ChT: Choroidal thickness. [a]There was a significant difference comparison baseline values.

Table 3 Distribution of macular thickness according to 9 ETDRS regions and comparison of these regions between groups mean (SD), μm

Regions	Controls (*n*=59)	Group 1 (*n*=22)	Group 2 (*n*=19)	Group 3 (*n*=18)	*P*
Center	236.0 (11.0)	238.8 (25.6)	239.6 (10.9)	259.4 (31.0)	0.148
Inner temporal	325.5 (32.1)	315.4 (28.8)	315.9 (29.1)	318.6 (24.4)	0.166
Inner superior	345.5 (17.2)	320.1 (32.9)	326.9 (17.2)	334.4 (25.2)	0.007
Inner nasal	340.6 (25.9)	323.7 (39.2)	327.3 (31.6)	329.5 (27.5)	0.062
Inner inferior	341.1 (32.3)	321.7 (31.7)	328.4 (23.3)	334.0 (25.5)	0.292
Outer temporal	292.4 (21.6)	280.7 (22.3)	282.3 (28.4)	284.5 (28.5)	0.597
Outer superior	301.7 (19.5)	287.9 (20.3)	298.9 (19.8)	300.2 (27.5)	0.230
Outer nasal	316.8 (23.0)	308.0 (26.6)	309.4 (17.5)	317.6 (20.6)	0.242
Outer inferior	296.6 (22.3)	287.4 (28.5)	288.0 (39.6)	285.2 (23.6)	0.395
Mean	310.6 (19.4)	298.2 (22.3)	301.3 (21.0)	306.7 (23.2)	0.148

ETDRS: Early Treatment Diabetic Retinopathy Study.

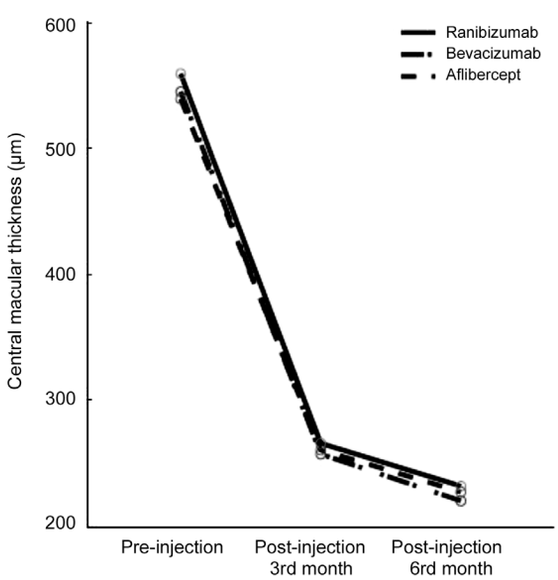

Figure 3 Decrease in CMT over time after injection of anti-VEGF agents.

is a challenging process because it can heal spontaneously, can be permanent, and can cause permanent damage to the macula and lead to a reduction in BCVA[12]. Nowadays, although there is no consensus between treatment options in IGS, intravitreal anti-VEGF injection is one of the commonly used second-line treatment modalities[5].

The anatomical and functional success of intravitreal anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept) in the treatment of refractory CME has been previously reported[7-8,10,13-14]. Although Spitzer achieved anatomical success other than visual function gain after bevacizumab[15], the results of the present study are in line with the results of previous studies. Further comparisons showed that these 3 different anti-VEGF agents have similar efficacy in the treatment of IGS. However, although the faster resolution of CME with intravitreal bevacizumab is an interesting finding, the lack of monthly follow-up of patients may have caused this result.

Table 4 Distribution of RNFL and GCL and comparison of these regions between groups mean (SD), μm

Rgeions	Controls (*n*=59)	Group 1 (*n*=22)	Group 2 (*n*=19)	Group 3 (*n*=18)	*P*
RNFL					
Whole	99.9 (18.0)	96.3 (21.1)	98.6 (12.2)	97.2 (16.5)	0.649
Superior	105.4 (16.0)	99.4 (18.3)	101.9 (16.2)	100.0 (15.2)	0.462
Inferior	100.0 (12.9)	89.9 (23.0)	99.3 (13.1)	96.3 (19.2)	0.255
Temporal	69.9 (17.3)	63.9 (8.6)	63.7 (11.2)	59.2 (6.3)	0.007[a]
Nasal	80.5 (25.2)	81.1 (9.3)	84.7 (25.8)	88.0 (20.7)	0.980
GCL					
Inner TS	114.2 (12.8)	100.0 (17.6)	101.4 (10.3)	104.3 (19.1)	0.0001[a]
Inner NS	122.5 (13.6)	107.5 (16.4)	110.7 (10.4)	110.5 (19.2)	0.0001[a]
Inner NI	122.5 (13.6)	105.0 (16.1)	112.4 (10.4)	114.2 (11.9)	0.001[a]
Inner TI	114.7 (13.7)	100.0 (14.8)	108.2 (9.5)	108.0 (9.5)	0.003[a]
Outer TS	90.4 (8.7)	87.9 (12.4)	90.0 (8.4)	88.3 (12.1)	0.483
Outer NS	112.7 (12.2)	105.2 (17.6)	112.2 (7.9)	110.0 (14.1)	0.165
Outer NI	113.9 (17.6)	104.5 (14.4)	110.5 (10.0)	107.0 (14.6)	0.013[a]
Outer TI	96.7 (14.3)	90.4 (9.8)	90.5 (10.8)	90.9 (15.2)	0.251
Mean	11.4 (12.0)	100.1 (13.6)	105.2 (6.1)	104.2 (8.4)	0.003[a]

RNFL: Retinal nerve fiber layer, GCL: Ganglion cell layer; TS: Temporal-superior; NS: Nasal-superior; NI: Nasal-inferior; TI: Temporal-inferior. [a]Statistically significant.

Noda *et al*[16] reported that subfoveal ChT was higher than baseline values in the majority of patients in the first 6mo after cataract surgery. Also, there are studies reporting that ChT increases during the acute postoperative period and then decreases to preoperative values[17-19]. It is not known whether this is due to rupture of the inner blood-retinal barrier by surgical trauma-induced prostoglandin release or as a result of rupture caused by inflammation of the outer blood-retinal barrier, or the increase of inflammatory cascades in all structures caused by surgical trauma[20-21]. Another theory is that it causes angiogenesis by increasing metabolic activity in RPE due to intense light entering the eye during surgery[22]. Fleissig *et al*[19] also mentioned the decrease in ChT, although it is still higher than the normal population after treatment. And they interpreted this situation as an inflammatory process. However, the types of treatment in their study (*e.g.* intravitreal aflibercept, subtenon triamcinolone, and topical steroid/non steroid drugs) differed[19]. Also, in the current study, ChT was significantly increased in patients with IGS, and after anti-VEGF treatment, it decreased to similar values with the healthy population. We believe that this is evidence that the choroidal inflammatory process is suppressed by anti-VEGF treatment in IGS patients. In addition, it was noteworthy that all three anti-VEGF agents had similar efficacy in suppressing choroidal inflammation.

In an OCT study, in which they defined macular edema due to different causes, Munk *et al*[23] showed that GCL was reduced in IGS related CME. In the same study, it was shown that RNFL thickness increased in IGS patients compared to the control group[23]. In an experimental study, it was shown that VEGF had a neuroprotective effect on the retinal ganglion cell, and this effect was eliminated with bevacizumab[24]. Shin *et al*[25] did not detect a significant change in RNFL thickness after multiple anti-VEGF injections in their study with age related macular degeneration, diabetic macular edema, and retinal vein occlusion patients. However, RNFL thickness decreased in all three patient groups. Using this approach, in the current study, the lower GCL thickness and the similar RNFL thickness after treatment compare with the control group can be explained by the effect of anti-VEGF agents.

This study has some limitations, primarily the small sample size and retrospective design. The lack of follow-up from the cataract surgery until the development of IGS and lack of follow-up in this period were among the limitations. The lack of randomization of the anti-VEGF agent among the patients was another limitation. In conclusion, all three anti-VEGF agents seem to be effective in IGS. However, bevacizumab appears to be slightly more cost-effective than the other two alternatives because it is cheaper.

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