Int Ophthalmol (2019) 39:891–901
https://doi.org/10.1007/s10792-018-0890-6

ORIGINAL PAPER

The short-term efficacy of intravitreal ranibizumab, aflibercept and dexamethasone implant in the treatment of macular edema due to non-ischemic central retinal vein occlusion

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Received: 7 June 2017 / Accepted: 13 March 2018 / Published online: 17 March 2018

Abstract

Purpose To assess and compare the efficacy over 6 months of intravitreal ranibizumab (IR), aflibercept (IA) and dexamethasone implant (IDI) in eyes with macular edema (ME) secondary to non-ischemic central retinal vein occlusion (CRVO).

Methods This is a retrospective single-center study. Patients who received pro re nata treatment of IR 0.5 mg, IA 2 mg or IDI 0.7 mg (as Group 1, Group 2, and Group 3, respectively) for the treatment of ME due to non-ischemic CRVO were included in the study. Efficacy outcomes were considered as the changes in mean best-corrected visual acuity (BCVA) and central macular thickness (CMT) from baseline over 6 months.

Results Eighteen patients (Group 1) received IR, 16 patients received (Group 2) IA, and 24 patients (Group 3) received IDI. The mean numbers of injections were 2.56 ± 1.0, 2.68 ± 0.9, and 1.62 ± 0.5 in Group 1, 2, and 3, respectively ($p = 0.000$). In Groups 1 and 2, the mean BCVA values increased significantly after the treatment ($p < 0.001$). However, in Group 3, no increase in mean BCVA was statistically significant in any month ($p = 0.061$). The proportion of eyes gaining at least three lines in BCVA was 33.3% in Group 1, 43.8% in Group 2, and 33.3% in Group 3 ($p = 0.762$). In all groups, significant improvements were observed in CMT after treatment ($p < 0.001$). At month 6, the mean changes in CMT were − 162.7 ± 186.5 µm in Group 1, − 310.1 ± 345.9 µm in Group 2, and − 193.8 ± 228.3 µm in Group 3, with no significant difference among groups ($p = 0.474$). Cataract formation and IOP increase were higher in the IDI group, but the differences were not statistically significant ($p = 0.054$ and $p = 0.392$, respectively).

Conclusions IR and IA may be preferred treatment for ME due to non-ischemic CRVO as visual improvement remains the primary ophthalmological objective. The most important advantages of IDI are its effect on CMT and the need for fewer injections. The increase in IOP and the formation of cataract may be observed more in IDI-treated eyes.

Keywords Aflibercept · Central retinal vein occlusion · Dexamethasone implant · Macular edema · Ranibizumab · Retinal vein occlusion

Introduction

Retinal vein occlusion (RVO) is a common, sight-threatening retinal vascular disorder, and the prevalence of central RVO (CRVO) is estimated to be 0.8 per 1000 [1]. In RVO, increased intravascular pressure in the venous bed leads to transudation of fluid into the

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extracellular space. The resulting edema is further accelerated by the release of vascular hyperpermeability agents, including vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine whose expression is increased in RVO [2]. Macular edema (ME) is the primary cause of poor visual acuity (VA) in non-ischemic CRVO, and resolution of ME leads to significant visual improvement [3].

Laser treatment has been found not to be beneficial in ME secondary to CRVO [4], and numerous other treatments have therefore been proposed, including various types of intravitreal anti-VEGF injections [5–7]. Anti-VEGF agents—such as bevacizumab, ranibizumab, and aflibercept—reduce ME by inhibiting VEGF-A. Ranibizumab is a recombinant humanized monoclonal antibody fragment that binds to and neutralizes all isoforms of VEGF-A [8, 9]. Aflibercept is a decoy receptor fusion protein that binds multiple isoforms of human VEGF-A, VEGF-B, and placental growth factor (PlGF) with high affinity [10, 11]. Corticosteroids—such as triamcinolone acetonide, dexamethasone, and fluocinolone—can also reduce ME through various mechanisms [12–14]: They have potent anti-inflammatory effects, they inhibit the synthesis of VEGF and cytokines and the migration of inflammatory cells, and they stabilize tight junctions between endothelial cells [15, 16].

The following drugs are currently approved for the treatment of ME due to CRVO: ranibizumab 0.5 mg injection (Lucentis®; Novartis Pharmaceuticals AG, Basel, Switzerland, and Genentech Inc, South San Francisco, California, USA) (IR); aflibercept 2 mg injection (Eylea® VEGF Trap-Eye; Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Bayer HealthCare Pharmaceuticals, Berlin, Germany) (IA); and dexamethasone intravitreal implant 0.7 mg (Ozurdex®; Allergan, Inc, Irvine, California, USA) (IDI). The aim of the present study is to assess and compare the safety and efficacy over 6 months of IR, IA, and IDI in eyes with ME secondary to non-ischemic CRVO.

Methods

This retrospective descriptive study was conducted at Ondokuz Mayis University Hospital, Samsun, Turkey. It was approved by the local Research Ethics Committee and carried out according to the principles outlined in the Declaration of Helsinki.

A review was carried out of the charts of consecutive treatment-naive patients who had received pro re nata (PRN) treatment of IR 0.5 mg, IA 2 mg, or IDI 0.7 mg for the treatment of ME due to non-ischemic CRVO. Patients who were followed up monthly for at least 6 months were included in the study. The criteria for exclusion from the study were: ME caused by any other ocular diseases; macular ischemia observed on fluorescein angiography; vitrectomized eye; follow-up period of less than 6 months; or missing data. CRVO was considered to be non-ischemic in the following conditions: fewer than 10 disk areas of non-perfusion; no neovascularization in the retina, optic disk, or anterior segment; and no afferent pupillary defect. Patients with baseline best-corrected visual acuity (BCVA) less than 2.0 logMAR were also excluded because of the possibility of ischemia: retinal ischemia may not be correctly evaluated due to intense retinal hemorrhage in its early stages, and poor VA is a clinical feature that may also suggest ischemic CRVO [3].

The following data were recorded: baseline demographic and ocular characteristics of the patients; ocular findings at follow-up visits; fluorescein angiography findings at baseline and at month 6; type and number of intravitreal injections; and any adverse events related to the injections. Baseline and follow-up visits recorded the following data: BCVA measurements (Snellen); slit-lamp biomicroscopy; dilated fundoscopy; intraocular pressure (IOP) measurements (Goldmann applanation tonometer); and central macular thickness (CMT) measurements from spectral domain optical coherence tomography (SD-OCT) (Zeiss Stratus 3; Carl Zeiss Meditec Inc., Dublin, CA). For the statistical analysis, VA was converted to the log of the minimum angle of resolution (logMAR). Intravitreal injections were administered as needed in the fourth week at the earliest. If the macula was dry on OCT, no reinjection was given. A second implantation was not administered in the first 3 months after IDI, even when ME was present. A second IDI was implanted in the fourth month at the earliest.

Patients who received IR, IA, and IDI were referred to as Group 1, Group 2, and Group 3, respectively. Efficacy outcomes were considered as the changes in mean BCVA and CMT from baseline over 6 months. In addition, the proportion of eyes gaining at least

three lines of BCVA was assessed. The safety outcome was considered as the incidence of side effects related to intravitreal injections.

Statistical analysis

The statistical analysis was carried out using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Because the data did not fit the normal distribution, the Kruskal–Wallis test and the Mann–Whitney U test with a Bonferroni correction were used for continuous independent variables. For these tests, p values of < 0.05 and ≤ 0.016, respectively, were considered to be statistically significant. A Chi-square test was used to compare categorical independent variables, and p value of < 0.05 was considered to be statistically significant. The Friedman test and Wilcoxon signed-rank test with a Bonferroni correction were used to compare changes in BCVA and CMT over time. For these tests, p values of < 0.05 and ≤ 0.002, respectively, were considered to be statistically significant. The results were given as mean ± standard deviation (minimum–maximum) and frequency (%).

Results

Patient demographics

Fifty-eight eyes of 58 patients were included in the study. Eighteen patients (Group 1) received IR, 16 patients (Group 2) received IA, and 24 patients (Group 3) received IDI. The mean BCVA and the mean duration of ME before treatment were both similar among the groups ($p > 0.05$). The mean CMT in Group 2 was higher than in Groups 1 and 3 ($p = 0.045$), but there were no statistically significant differences in the binary comparisons of groups ($p > 0.016$). Four patients in Group 1 (22.2%) had glaucoma, but no patients in Groups 2 or 3 had glaucoma at baseline ($p = 0.009$). All three groups had similar rates of lens opacity and pseudophakia. Baseline characteristics of the patients are presented in Table 1.

The mean numbers of injections in the six-month follow-up period were as follows: 2.56 ± 1.0 (1–5) in Group 1, 2.68 ± 0.9 (1–4) in Group 2, and 1.62 ± 0.5 (1–2) in Group 3 ($p = 0.000$). The mean number of injections in Group 3 was statistically lower than in Groups 1 and 2 ($p = 0.000$). The mean application time of the second IDI in Group 3 was 4.7 ± 0.8 (4–6) months. There was no difference between Groups 1 and 2 in the number of injections ($p = 0.539$).

Changes in visual acuity

In Groups 1 and 2, the mean BCVA values increased significantly after treatment ($p < 0.001$). In Group 1, the differences from baseline were statistically significant in months 1, 2, 3, and 4 ($p = 0.002$); in Group 2, the differences were significant in months 1, 2, and 3 ($p = 0.001$, 0.001, and 0.002, respectively). There was no significant further improvement in mean BCVA values in Groups 1 and 2 after the first month ($p > 0.002$). In Group 3, no increase in mean BCVA was statistically significant in any month ($p = 0.061$). The mean BCVA values are presented in Table 2. The mean BCVA values were not statistically different among the groups in any month ($p > 0.05$).

The proportion of eyes gaining at least three lines in BCVA was 33.3% in Group 1, 43.8% in Group 2, and 33.3% in Group 3 ($p = 0.762$). The proportion of eyes gaining less than three lines in BCVA was 50.0% in Group 1, 37.5% in Group 2, and 33.3% in Group 3 ($p = 0.539$). The proportion of eyes losing at least one line in BCVA was 11.1% in Group 1, 6.3% in Group 2, and 20.8% in Group 3 ($p = 0.392$). BCVA changes are presented in Table 3.

Changes in macular thickness

In all groups, significant improvements were observed in CMT after treatment ($p < 0.001$). The differences in mean CMT from baseline were statistically significant in all groups at all months ($p \leq 0.002$), except for Group 2 at month 6. There were no significant further improvements in mean CMT values after the first month in any group ($p > 0.002$). The mean CMT values are presented in Table 4. The mean CMT values were not statistically different among the groups at any month ($p > 0.05$). At month 6, the mean changes in CMT were −162.7 ± 186.5 µm in Group 1, −310.1 ± 345.9 µm in Group 2, and −193.8 ± 228.3 µm in Group 3, with no significant difference among groups ($p = 0.474$). CMT changes are presented in Table 3.

Table 1 Baseline characteristics of the patients

Characteristic	Ranibizumab (n = 18)	Aflibercept (n = 16)	Dexamethasone (n = 24)	p
Age (years)	61.2 ± 2.8	66.2 ± 3.2	65.4 ± 2.3	0.390
Systemic diseases				
Hypertension	6 (33.3%)	9 (56.3%)	14 (58.3%)	0.239
Diabetes	5 (27.8%)	8 (50%)	8 (33.3%)	0.382
Hyperlipidemia	0	1 (6.3%)	2 (8.3%)	0.476
Ocular diseases				
Glaucoma	4 (22.2%)	0	0	0.009*
Cataract	1 (5.6%)	3 (18.8%)	7 (29.2%)	0.160
Pseudophakia	0	4 (25%)	3 (12.5%)	0.086
ME duration (months)	3.38 ± 2.8	5.31 ± 5.1	5.04 ± 4.3	0.812
BCVA, logMAR	0.91 ± 0.44	1.14 ± 0.50	1.11 ± 0.46	0.301
CMT (μm)	587.8 ± 140.9	782.8 ± 248.8	668.7 ± 193.5	0.045*

Values are mean ± standard deviation or n (%)

BCVA best-corrected visual acuity, *CMT* central macular thickness; *logMAR* log of the minimum angle of resolution, p Kruskal–Wallis test for continuous variables and Chi-square test for categorical variables

*Statistically significant result

Table 2 The mean best-corrected visual acuity values (logMAR)

Month	BCVA					
	Ranibizumab	p	Aflibercept	p	Dexamethasone	p
0	0.91 ± 0.44		1.14 ± 0.50		1.11 ± 0.46	
1	0.54 ± 0.33	0.002*	0.79 ± 0.49	0.001*	0.90 ± 0.54	0.028
2	0.60 ± 0.31	0.002*	0.71 ± 0.50	0.001*	0.95 ± 0.57	0.184
3	0.60 ± 0.37	0.002*	0.78 ± 0.51	0.002*	0.99 ± 0.59	0.432
4	0.59 ± 0.38	0.002*	0.84 ± 0.64	0.023	0.98 ± 0.69	0.458
5	0.67 ± 0.42	0.014	0.85 ± 0.63	0.028	0.94 ± 0.67	0.206
6	0.71 ± 0.49	0.050	0.87 ± 0.64	0.046	1.00 ± 0.64	0.541

Values are mean ± standard deviation

BCVA best-corrected visual acuity, p Wilcoxon signed ranks test with a Bonferroni correction. Comparison with baseline value for BCVA

*Statistically significant result

Development of ischemia

At the end of 6 months of follow-up, large peripheral non-perfusion area had developed in three eyes in Group 1 (16.7%), in six eyes in Group 2 (37.5%), and in seven eyes (29.2%) in Group 3 (p = 0.388). In eyes without ischemia, the rates of BCVA improvement of at least three lines at month 6 were 40.0% for Group 1, 60.0% for Group 2, and 47.1% for Group 3 (p = 0.617). In eyes with ischemia, at least three lines gain in BCVA was seen in one eye in Group 2 (16.7%), but in no eyes in either Group 1 or Group 3. In eyes with and without ischemia, BCVA and CMT changes are presented in Table 3.

Table 3 Six month treatment outcomes

	Ranibizumab	Aflibercept	Dexamethasone	*p*
Number of eyes (*n*)				
Total	18	16	24	
Eyes without ischemia	15	10	17	0.388
Eyes with ischemia	3	6	7	
BCVA gaining $\geq$ 3 lines (%)				
Total	33.3	43.8	33.3	0.762
In eyes without ischemia	40.0	60.0	47.1	0.617
In eyes with ischemia	0.0	16.7	0.0	0.411
BCVA gaining $<$ 3 lines (%)				
Total	50.0	37.5	33.3	0.539
In eyes without ischemia	53.3	30.0	29.4	0.317
In eyes with ischemia	33.3	50.0	42.9	0.891
BCVA losing $\geq$ 1 line (%)				
Total	11.1	6.3	20.8	0.392
In eyes without ischemia	6.7	0.0	11.8	0.516
In eyes with ischemia	33.3	16.7	42.9	0.595
Changes in CMT (μm) (mean ± SD)				
Total	−162.7 ± 186.5	−310.1 ± 345.9	−193.8 ± 228.3	0.474
In eyes without ischemia	−122.9 ± 155.3	−372.5 ± 338.7	−199.1 ± 160.5	0.156
In eyes with ischemia	−361.7 ± 235.4	−206.0 ± 362.8	−181.0 ± 361.8	0.612
Cataract (%)				
Total	5.6	6.3	29.2	0.054
In eyes without ischemia	6.7	0.0	29.4	0.062
In eyes with ischemia	0.0	16.7	28.6	0.562
A rise in IOP $>$ 25 mmHg (%)				
Total	11.1	6.3	20.8	0.392
In eyes without ischemia	6.7	0.0	17.6	0.287
In eyes with ischemia	33.3	16.7	28.6	0.827

BCVA best-corrected visual acuity; *CMT* central macular thickness; *SD* standard deviation; *IOP* intraocular pressure; *p* Kruskal–Wallis test for continuous variables and Chi-square test for categorical variables

Table 4 The mean central macular thickness values (μm)

Month	CMT					
	Ranibizumab	*p*	Aflibercept	*p*	Dexamethasone	*p*
0	587.8 ± 140.9		782.8 ± 248.8		668.7 ± 193.5	
1	249.1 ± 39.3	0.000*	383.6 ± 271.9	0.002*	331.5 ± 190.9	0.000*
2	369.9 ± 213.4	0.001*	355.1 ± 226.4	0.001*	333.5 ± 145.1	0.000*
3	340.8 ± 140.3	0.001*	383.9 ± 279.5	0.002*	353.5 ± 141.1	0.000*
4	326.9 ± 188.4	0.000*	376.6 ± 186.0	0.001*	476.0 ± 323.4	0.002*
5	381.4 ± 189.4	0.001*	333.1 ± 131.5	0.000*	320.6 ± 146.9	0.000*
6	424.9 ± 208.4	0.002*	472.7 ± 266.8	0.004	474.8 ± 242.6	0.000*

Values are mean ± standard deviation

CMT central macular thickness, *p* Wilcoxon signed ranks test with a Bonferroni correction. Comparison with baseline value for CMT

*Statistically significant result

Safety outcomes

Cataract developed in one phakic eye in Group 1 (5.6%), in one phakic eye in Group 2 (6.3%), and in seven phakic eyes in Group 3 (29.2%) ($p = 0.054$). A rise in IOP to > 25 mmHg was observed in two eyes in Group 1 (11.1%), in one eye in Group 2 (6.3%), and in five eyes in Group 3 (20.8%) ($p = 0.392$). In all cases, the rise in IOP was managed with topical IOP-lowering medication. The rates of cataract development and IOP rise are presented in Table 3. No systemic side effects were detected in any patient.

Discussion

Intravitreal therapies consisting of anti-VEGF agents and steroids are currently used in the treatment of ME due to CRVO. In this study, we investigated the outcomes of IR, IA, and IDI in real-life conditions. Increases in mean BCVA were significant in the IR and IA groups, but not in the IDI group. There were no statistically significant differences among the treatment agents in the proportions of eyes with at least three lines of BCVA improvement, in the proportions of eyes with less than three lines of BCVA improvement, or in any BCVA decrease. There was a significant decrease in CMT in all groups, and no differences among the groups. Cataract formation and IOP increase were higher in the IDI group, but the differences were not statistically significant.

VEGF plays a key role in the pathophysiology of CRVO and its sequelae. Several anti-VEGF treatments have been developed with the aims of decreasing VEGF and blocking vascular permeability and angiogenic activity [17] (Table 5). In the CRUISE and ROCC studies, IR 0.5 mg produced greater improvements in BCVA in 6 months than sham in the treatment of ME due to CRVO [6, 18]. In the current study, the percentage of patients who gained 15 letters in BCVA was lower than in the CRUISE study. However, the patients in the CRUISE study received monthly injections of IR, whereas the patients in the current study received the PRN injections. In the ROCC study, there was a worsening of BCVA score and an increase in CMT at month 4 in the IR group, because an injection was administered only if there was ME in the OCT after month 3. The authors of the ROCC study therefore commented that it would be necessary for some patients to receive repeated monthly injections in order to maintain anatomical and visual improvements in the first 6 months of treatment with 0.5 mg IR [18]. In the HORIZON trial, patients who completed the CRUISE study were examined at least once every 3 months and were given an IR if they met prespecified criteria for retreatment [6, 19]. The results of that study showed a decline in vision in CRVO patients, suggesting that follow-up and injections should be individualized during the second year of IR treatment, and that patients may require follow-up more frequently than once every 3 months [20]. The rate of serious cataract formation was low in the CRUISE and HORIZON studies [6, 19].

The COPERNICUS trial investigated aflibercept in patients with ME resulting from CRVO [7, 20]. At 24 weeks, monthly intravitreal injections of IA 2 mg improved VA and CMT and eliminated the progression resulting from neovascularization. Baseline perfusion status did not affect response rates [7]. In the current study, the proportion of patients gaining at least 15 letters was less than in the COPERNICUS trial, and the proportion losing at least five letters was slightly higher than in the COPERNICUS trial (6.3 vs. 4.4%). From weeks 24 to 52, the visual and anatomical improvements continued after PRN dosing with monthly monitoring, but from weeks 52 to 100, they diminished after PRN dosing with reduced monitoring frequency in the COPERNICUS trial. In order to reduce the burden of monitoring and to maintain the gains achieved with monthly injections, the authors of the COPERNICUS trial proposed a treat-and-extend regimen, or a fixed every-two-months dosing regimen of IA following an initial period of monthly doses [20].

In the GENEVA study, in patients receiving IDI 0.7 mg, significant differences compared to sham were demonstrated for the proportion of patients gaining at least 15 letters at months 1 and 2, but the difference was not significant at month 6 [13] (Table 5). In the current study, this ratio was higher than for the CRVO patients in the GENEVA study. The authors of the GENEVA study proposed that 180 days may not be long enough to detect any effect of treatment on cataract formation [13]. They reported an increase in IOP to > 25 mmHg at 2 months in about 16% of IDI-treated eyes. The increases were transient, and by day 180, there were no differences between the IDI groups and the sham group [13]. In the

Table 5 Study characteristics, efficacy and safety results

Study (year) [Ref.]	Product	Treatment regimen	Follow-up (months)	Mean number of injections	Change from baseline BCVA (letters)	Proportion of eyes gaining ≥ three lines of BCVA (%)	Cataract progression rate (%)	IOP increases rate (%)
CRUISE (2010) [6]	R 0.3 and 0.5 mg	Monthly for 6 months	6	5.7	+ 12.7 and + 14.9	46.2 and 47.7	1.5 and 1.6	No
ROCC (2010) [18]	R 0.5 mg	Monthly for 3 months then PRN	6	4.3	+ 12.0	NR	No	No
HORIZON[a] (2012) [19]	R 0.5 mg	PRN every 3 months	24 (12)[ϕ]	12.3 (3.5)[ϕ]	+ 12.0 (− 4.1)[ϕ]	45.1	7	0.9
COPERNICUS (2012) [7]	A 2 mg	Monthly for 6 months	6	6	+ 17.3	56.1	No	No
COPERNICUS (2014) [20]	A 2 mg	Monthly for 6 months then PRN	24 (12)[ϕ]	12 (3.3)[ϕ]	+ 13.0 (− 3.2)[ϕ]	49.1	2.7	No
GENEVA (2010) [13]	D 0.7 mg implant	Every 6 months	6	1	No[a]	22[a]	7.3	16
Joshi et al.[a] (2013) [21]	D 0.7 mg implant	PRN every 3 months	12	1.9	11.5	38	3.6	27
Querques et al. (2013) [22]	D 0.7 mg implant	PRN	NR	NR	NR	34.6[a]	36.4	24.2
COMRADE-C (2016) [23]	R 0.5 mg	Monthly for 3 months then PRN	6	4.5	+ 16.9	58.9	No	5.6
	D 0.7 mg implant	Every 6 months		1	− 0.7	18.5	0.8	31.9
Nghiem-Buffet et al. (2014) [24]	R 0.5 mg	Monthly for 3 months then PRN	18.4[a]	7.7[a]	+ 18.2[a]	NR	No	No
	D 0.7 mg implant	PRN	11.4[a]	1.9[a]	+ 16.8[a]	NR	2.4	17
Chatziralli et al. (2017) [28]	R 0.5 mg	Monthly for 3 months then PRN	18	6.8	+ 7.9	35.3	No	No
	A 2 mg			6.1	+ 7.4	32.1	No	No
Current study	R 0.5 mg	PRN	6	2.6	− 0.2 (logMAR)	33.3	5.6	11.1
	A 2 mg			2.7	− 0.27 (logMAR)	43.8	6.3	6.3
	D 0.7 mg implant	PRN every 4 months		1.6	− 0.11 (logMAR)	33.3	29.2	20.8

Ref. Reference, *R* ranibizumab, *A* aflibercept, *D* dexamethasone

[ϕ]Month 24 result (month 12–24 result)

[a]Results of CRVO patients (for the studies included both BRVO and CRVO patients)

current study, rates of elevated IOP and cataract in IDI-treated eyes were higher than in the GENEVA study, perhaps due to the low number of patients. The IOP increases were transient, and they were controlled in all eyes with topical IOP-lowering medication.

Joshi et al. [21] reported that 72% of eyes with CRVO responded to IDI, with an improvement in VA and ME within 3 months of injection. The median time for the relapse of ME was 18 weeks. Querques et al. [22] evaluated the effects of repeated IDI in 33 eyes with ME due to RVO (26 of them with CRVO). They found an improvement in CMT and at least three lines of improvement from baseline BCVA in 30.3% of eyes. The current study found rates of visual improvement and cataract development similar to those found in Joshi's and Querques's studies.

Only a few studies have compared the medications currently used in the treatment of ME secondary to RVO. These study characteristics and results are shown in Table 5. The COMRADE-C study is the first head-to-head phase IIIb study to compare the efficacy and safety of the European labels of IR and IDI in patients with visual impairment due to ME secondary to CRVO. In the COMRADE-C study, similar efficacy was observed for IR and IDI in months 1 and 2. Ranibizumab maintained its efficacy throughout the study, whereas IDI declined from month 3 onward. However, it is important to note that the IDI group received only a single treatment during the 6 months of the study. Improvements in BCVA were paralleled by a significant reduction in mean foveal center point thickness from baseline with IR versus IDI. Adverse ocular events were more frequent in the IDI group than in the IR group [23]. Nghiem-Buffet et al. have shown that IR and IDI are beneficial for the treatment of ME secondary to RVO in real-life conditions, and they therefore propose using both drugs as first-line therapy. They also found extensive peripheral ischemia in 38.5% of patients with CRVO [24]. In the current study, the decrease in CMT was significant with both IR and IDI. Nevertheless, the improvements in BCVA were paralleled by a reduction in mean CMT with IR only and not with IDI. This suggests that the efficacy of IDI is more anatomical than functional. Although the cause is not clear, anti-VEGF agents led to a better gain in BCVA than steroids at 1 year in the treatment of ME due to CRVO (+ 16.2 letters with IA in the COPERNICUS study, + 13.9 letters with IR in the CRUISE study, and + 2 letters with IDI in the GENEVA study) [25–27]. Changes in CMT may not be the only factors affecting VA in ME due to CRVO. Modulation by anti-VEGF drugs of circulation in the retina may also contribute to improvements in VA. Chatziralli et al. found similar anatomical and functional outcomes with IR and IA over an 18-month follow-up period, and they observed no serious ocular or systemic side effects. In addition, 23.5% of the patients in their IR group and 25% in their IA group had ischemic CRVO at baseline [28]. Likewise, in the current study, IR and IA were similar in efficacy, and no serious ocular or systemic side effects were observed with either agent.

A number of studies have carried out indirect comparisons of medications currently used in the treatment of ME secondary to RVO. For example, a review of IR and steroids recommended a course of six injections of 0.5 mg IR at monthly intervals. After month 6, it was stated it is best to continue monthly follow-up visits and IR injections for recurrent edema in CRVO for at least 1 year [29]. In a systematic review which reported 12 months of data for five different therapeutic intravitreal agents, the greatest gains in VA were observed with IA 2 mg and bevacizumab 1.25 mg (+ 16.2 and + 16.1 letters, respectively). Ranibizumab 0.5 mg improved vision by + 13.9 letters. In this indirect comparison between steroids and anti-VEGF agents, the cataract progression (19.8–35.0 vs. 0.9–7.0%) and the treatment requirement for increased intraocular pressure (7.0–41.0% vs. none) were both higher in steroid-treated patients. However, the authors emphasized one advantage of steroid implants, namely the lower frequency of injections [30]. The current study also found that the proportion of patients gaining at least 15 letters and losing at least five letters was better with IA, although the differences were not statistically significant. These results suggest that anti-VEGF agents may be preferred as the first-line treatment for ME due to CRVO. A network meta-analysis reported no evidence of differences among ranibizumab, bevacizumab, aflibercept, and triamcinolone for improving vision in the treatment of ME secondary to CRVO, although dexamethasone was found to be less effective than those other drugs. As a result, the authors proposed that anti-VEGFs are likely to be favored, because they are not associated with steroid-induced cataract formation and that the clinicians may

prefer aflibercept, because it might require fewer injections [31].

In the Central Vein Occlusion Study, 15% of 547 eyes with perfusion converted to ischemia in the first 4 months of follow-up. Overall, 34% of initially perfused eyes converted to non-perfused status after 3 years. The development of ischemia was most rapid in the first 4 months, and it progressed continuously for the duration of the follow-up. Thirty-eight eyes (83%) with an indeterminate CRVO at baseline were ultimately determined to be non-perfused [32]. Hayreh et al. [33] reported that the probability of conversion of non-ischemic to ischemic CRVO at 6 months was 13.2% in persons aged 65 or older, and 6.7% in persons aged 45–64. In this series, rate of ischemic progression is higher than in the literature, perhaps due to undetermined eyes being mistakenly evaluated as perfused at baseline. Additionally, wide-field imaging was not used, and it is therefore possible that significant peripheral non-perfusion was present in some patients, despite their being classified as perfused. It is not known whether anti-VEGF treatment alters the extent of retinal non-perfusion. Wykoff et al. [34] stated that capillary dropout may be unaffected by anti-VEGF treatments and progress in retinas where the arterial circulation is severely compromised secondary to the venous blockage. The precise mechanism for improved perfusion in treated CRVO eyes is uncertain. Singer et al. [35] suggested that a proportion of circulation is closed, but not permanently, and that this closure is modulated by VEGF. Treatment with anti-VEGF could therefore result in reperfusion. Campochiaro et al. [36] reported that reperfusion of non-perfused retina occurred in 6–8% of CRVO patients treated with ranibizumab, but in only 1% of sham-treated patients. They suggested that VEGF exacerbates retinal ischemia by increasing leukostasis and that intravitreal anti-VEGF agents may break the feedback loop, allowing reperfusion to occur. Joshi et al. [21] speculated that steroid-induced ocular hypertension may further compromise retinal circulation, thus converting a non-ischemic CRVO into an ischemic CRVO. However, the proportion of ischemia progression in the anti-VEGF treatment groups was not found to be lower in the current study.

The current study reveals that PRN treatments of IR and IA have a beneficial effect on VA in ME secondary to non-ischemic CRVO. This effect was maintained for 4 months with IR and for 3 months with IA. All three drugs, IR, IA, and IDI, have a significant effect on CMT and are well tolerated. The limitations of this study are the short follow-up time, the relatively small number of patients, and the fact that patients were not randomized in terms of presence of glaucoma at baseline. The patients may have been under-treated, because the treatment of IR and IA was PRN, and because the second IDI application was provided no earlier than the fourth month, even when ME was present. In other CRVO studies with anti-VEGF agents, patients received monthly injections of IR and IA for 6 months [6, 7]. Therefore, six injections of IR 0.5 mg at monthly intervals were recommended for ME due to RVO [29]. It is also recommended that the interval between the two IDI injections should be less than 6 months [22]. In conclusion, as visual improvement remains the primary ophthalmological objective, IR and IA may be the preferred treatment for ME due to non-ischemic CRVO. The most important advantages of IDI are its effect on CMT and the need for fewer injections. The increase in IOP and the formation of cataract can be observed more in IDI-treated eyes.

Acknowledgments We thank Ozlem Terzi, M.D. for assistance in clinical information analysis.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Ethical standards This study was approved by the Ondokuz Mayis University Clinical Research Ethics Committee.

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